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REVIEW

Path of Pyrazoles from Synthetic Factors to Anti-inflammatory Potential

KETAN VASHISHT[1], POOJA SETHI[1,*], ANSHUL BANSAL[2], HARDEEP SINGH TULI[3], AMMAR ABDULRAHMAN JAIROUN[4,5], MOYAD SHAHWAN[6,7], SEEMA RAMNIWAS[8] and RITU CHAUHAN[9]

[1]Department of Chemistry, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala-133207, India
[2]Department of Chemistry, S.A. Jain College, Ambala City-134003, India
[3]Department of Bio-Sciences and Technology, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala-133207, India
[4]Health and Safety Department, Dubai Municipality, Dubai 67, Dubai, United Arab Emirates
[5]Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia (USM), Pulau Pinang, 11500, Malaysia
[6]Department of Clinical Sciences, College of Pharmacy and Health Sciences, Ajman University, Ajman 346, United Arab Emirates
[7]Centre of Medical and Bio-Allied Health Sciences Research, Ajman University, Ajman 346, United Arab Emirates
[8]University Centre for Research & Development, University Institute of Pharmaceutical Sciences, Chandigarh University, Gharuan, Mohali-140413, India
[9]Department of Biotechnology, Graphic Era Deemed to be University, Dehradun-248002, India

*Corresponding author: E-mail: pooja.amb80@gmail.com; sethipuja1001@gmail.com

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Pyrazoles, a class of heterocyclic compounds, have garnered considerable attention in drug development due to their intriguing properties, particularly those containing a pyrazole moiety. Pyrazole, a pivotal chemical in the creation of potent bioactive agents, encompasses five heterocyclic members. The discovery of certain pyrazole compounds exhibiting robust biological activities has spurred interest in this field of inquiry. Heterocyclic compounds incorporating nitrogen and its derivatives have historically served as crucial sources of medicinal compounds. Given that the heterocyclic group constitutes a vast reservoir of organic molecules, its significance in both theoretical and applied chemistry has grown significantly. Extensive literature indicates that researchers have employed diverse synthetic strategies in recent years to produce substituted pyrazole derivatives with promising biological potential as anti-HIV, anti-inflammatory, antitumor and antimicrobial agents. Inflammation, a multifaceted biological response essential for the body's defense mechanisms, can also contribute to various pathological conditions when dysregulated. Understanding the underlying molecular mechanisms offers a foundation for targeted interventions against inflammatory disorders. These insights fuel ongoing endeavors to discover effective and innovative anti-inflammatory agents with potential therapeutic applications. This review delves into the synthesis and characterization of various pyrazole derivatives, emphasizing structural modifications influencing their anti-inflammatory efficacy. The insights provided herein are invaluable for the rational design and synthesis of novel anti-inflammatory agents. Furthermore, the review concludes with a discussion on future perspectives, underscoring the imperative for further research to optimize the therapeutic potential of pyrazole derivatives as anti-inflammatory agents.

Keywords: Pyrazole, Anti-inflammatory antitumor, Anti-HIV, Antimicrobial agents.

INTRODUCTION

Heterocycles, comprising nitrogen-containing compounds, notably constitute approximately 85% of all FDA-approved medications aimed at combating inflammation, though this figure may fluctuate with the advent of new treatments. Compounds featuring diverse ring systems such as pyridine [1-3], pyrimidine [4-8], pyrazole [9,10], pyrazoline-pyrazolone [11-13], among others [14-18], have long been investigated for their medicinal potential, serving as foundational elements for pharmacologically active drugs. Pyrazole derivatives have garnered significant attention globally due to their versatile applications

spanning pharmaceuticals [19-21], agrochemistry [22-27] and various other industries. These compounds play a pivotal role in medicinal chemistry, serving as indispensable building blocks for innovative drug development [28-30].

The term "NSAID" refers to non-steroidal anti-inflammatory drugs, many of which are pyrazole derivatives [31]. Notably, celecoxib, the first sulfonamide and a COX-2 inhibitor derived from pyrazoles, is employed to reduce the inflammation and pain [32,33]. Inflammation, a fundamental process in vascular tissues triggered by various stimuli, including infections, cellular damage or irritants, is implicated in the diverse conditions such as autoimmune disorders, infections, cancer [34-36] and neurodegenerative diseases. NSAIDs, by inhibiting the activity of the COX enzyme crucial for prostaglandin production [37], are widely used to manage pain, fever and inflammation. Common side effects associated with NSAID use include indigestion, gastric ulceration, anemia and renal function suppression due to the high selectivity of COX-1 *versus* COX-2 [38,39]. While COX-1 is involved in homeostatic functions, COX-2 is primarily associated with inflammation and disease pathogenesis, including cancer. Efforts to enhance therapeutic efficacy and mitigate adverse effects have focused on developing potent and selective COX-2 inhibitors [40-45]. However, challenges persist in developing safer anti-inflammatory drugs due to the complex and multifactorial nature of inflammation in various diseases [46]. These challenges have prompted exploration into novel approaches for inflammation treatment [47].

This review article focuses into the synthesis methodologies and pharmacological properties of heterocyclic systems formed from pyrazoles, providing important insights into the development of anti-inflammatory drugs.

Biological relevance of heterocyclic compounds based on pyrazole motif: The term "heterocyclic" signifies that a compound contains at least one ring structure, with the prefix "hetero" indicating the presence of noncarbon atoms, known as heteroatoms, within the ring [48,49]. Heterocyclic compounds are prevalent in nature and are vital to life, playing essential roles in the metabolism of all living cells. Moreover, genetic materials like DNA consist of heterocyclic bases, including pyrimidines and purines. Biomolecules such as enzymes, vitamins and natural products, as well as biologically active compounds like anti-inflammatory, anticonvulsant, antifungal agents, antimicrobials, antibacterials, *etc.* commonly contain heterocycles in large proportions [50].

Through extensive literature review, pyrazoles have emerged as versatile compounds capable of exhibiting a wide array of biological actions (Fig. 1). These actions include anti-inflammatory [51,52], antifungal [53], antitubercular [54,55], anticonvulsant [56], antimicrobial [57,58], anticancer [59-61], cholecystokinin-1 receptor antagonist, angiotensin-converting enzyme (ACE) inhibition [62,63], estrogen receptor (ER) ligand activity [64,65] and more.

Molecular basis of pyrazole's anti-inflammatory effects: The anti-inflammatory properties of pyrazole, a chemical compound, stem from its interactions with various cellular and molecular targets involved in the inflammatory response. Although the exact mechanism of action may vary depending on specific

Fig. 1. Biological activity of pyrazoles

derivatives and experimental conditions [66], several general ways in which pyrazole compounds exert their anti-inflammatory effects have been identified:

Inhibition of pro-inflammatory enzymes: Pyrazole derivatives have been shown to inhibit enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), which play pivotal roles in synthesizing pro-inflammatory mediators like prostaglandins and leukotrienes. By blocking these enzymes, pyrazole can decrease the production of inflammatory eicosanoids [67,68].

Suppression of pro-inflammatory cytokines: Pyrazole compounds may modulate the expression and release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6). Pyrazole can mitigate inflammatory activity by inhibiting the action of these cytokines [69].

Inhibition of NF-κB activation: Nuclear factor-kappa B (NF-κB), a transcription factor, plays a critical role in controlling the expression of inflammatory genes. Pyrazole compounds have the potential to impede NF-κB activation, thereby reducing the transcription of genes that promote inflammation [70-72].

Modulation of immune cell function: Pyrazole derivatives may influence the function of immune cells implicated in the inflammatory response, such as neutrophils and macrophages. This modulation can involve the suppression of phagocytosis, migration and the release of inflammatory agents [73,74].

Reduction of vasodilation: Vasodilation, which increases blood flow to inflamed areas, is a common response to inflammation. Pyrazole compounds have been shown to reduce vasodilation and regulate the inflammatory response [75-77]. The specific mechanism of action depends on the structure of pyrazole compounds and requires further investigation to fully understand how they exert their anti-inflammatory actions for

potential therapeutic applications. Researchers continue to explore this topic to uncover the intricacies of pyrazole-mediated anti-inflammatory effects.

Anti-inflammatory drugs featuring pyrazole moieties: Medications containing pyrazole are renowned for their anti-inflammatory properties, widely utilized by pharmaceutical companies to alleviate inflammation. These medications often operate by modulating specific pathways and factors related to the inflammatory response. Some examples of pyrazole containing medications with anti-inflammatory actions *viz.* celecoxib, a non-steroidal anti-inflammatory drug (NSAID), features a pyrazole ring and selectively inhibits the enzyme cyclooxygenase-2 (COX-2), crucial for producing inflammatory prostaglandins. It is prescribed to alleviate pain and inflammation associated with conditions like osteoarthritis and rheumatoid arthritis [78]. Indomethacin, another traditional NSAID incorporating a pyrazole ring, inhibits both COX-1 and COX-2, thereby curtailing the production of inflammatory prostaglandins [79]. Etoricoxib, a selective COX-2 inhibitor with a pyrazole ring, suppresses the synthesis of pro-inflammatory prostaglandins. It is used in treating osteoarthritis, rheumatoid arthritis and acute gouty arthritis [80]. Tofacitinib, a Janus kinase (JAK) inhibitor containing a pyrazole ring, disrupts signaling pathways implicated in immune response and inflammation [81]. Aminoguanidine, which contains a pyrazole ring, serves as an inhibitor of inducible nitric oxide synthase (iNOS), contributing to its anti-inflammatory effects [82]. Aminoguanidine has garnered attention for its potential in managing chronic inflammatory conditions [83].

It is essential to recognize that while these drugs may share a pyrazole ring and possess anti-inflammatory effects, their mechanisms of action and clinical applications can differ. Moreover, ongoing advancements in drug development may unveil new pyrazole-containing compounds with anti-inflammatory properties. Structures of some FDA drugs with pyrazle motif for anti-inflammatory purposes are shown in Fig. 2.

Synthetic pathways of pyrazole derivatives in the context of anti-inflammatory studies: The synthetic methodologies concerning pyrazoles encompass various techniques and approaches for preparing compounds containing the pyrazole ring. Extensively studied, pyrazole synthesis has yielded diverse synthetic routes, owing to the pivotal role of pyrazoles as a

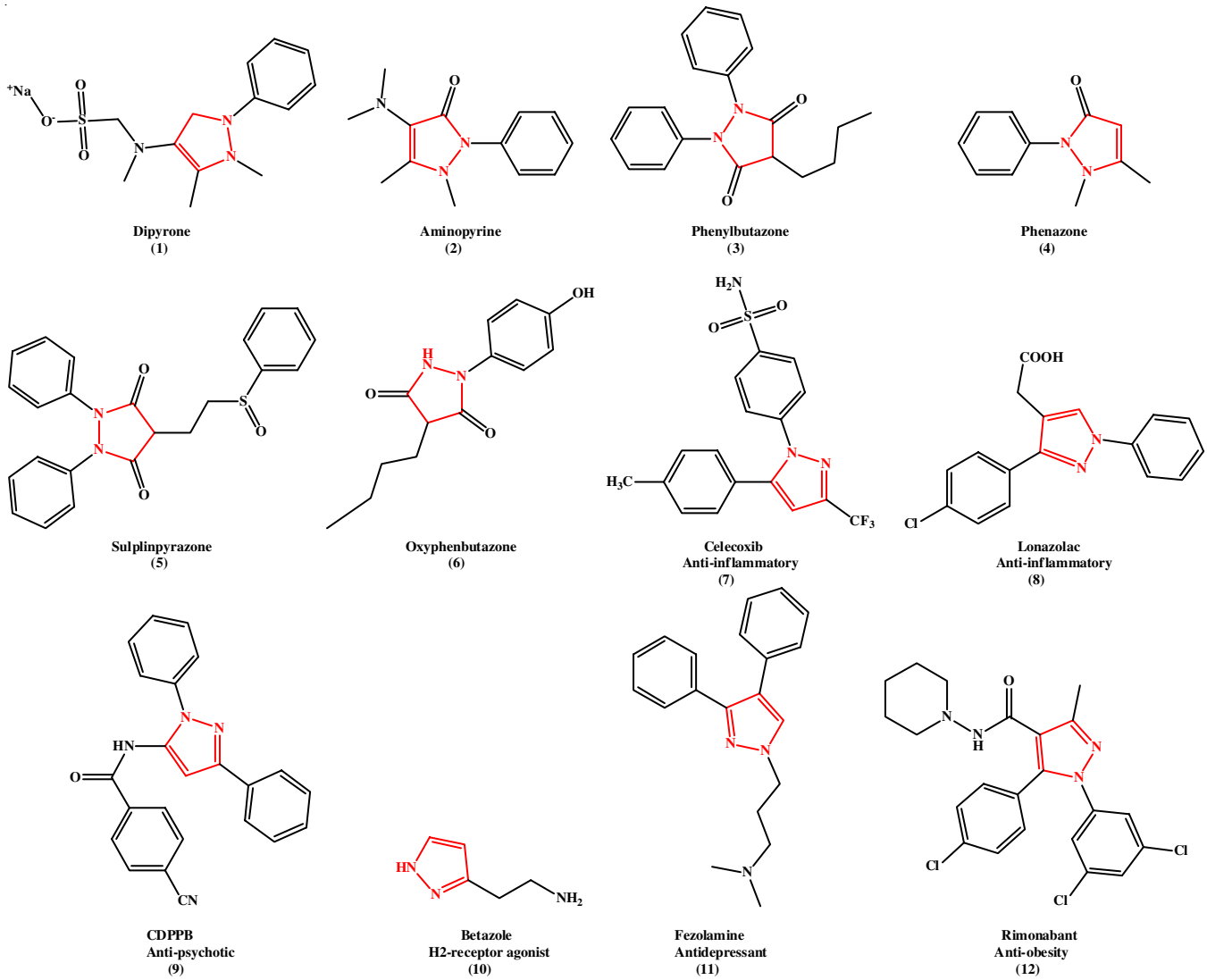


Fig. 2. Structures of some FDA approved drugs containing pyrazole moiety available in the market

fundamental scaffold within the azole family, associated with a spectrum of biological activities. This study aims to elucidate detailed synthesis procedures alongside comprehensive analyses of pyrazole's anti-inflammatory properties.

Li *et al*. [84] successfully synthesized a novel series of diaryl pyrazole derivatives, investigating their potential anti-inflammatory behaviour. Significantly, compound **13l** exhibited remarkable inhibition at 93.59%, surpassing the inhibitory effects of the reference standard drugs ibuprofen and indomethacin, which demonstrated inhibitions at 29.56% and 45.23%, respectively. Furthermore, compounds **13h**, **13m** and **13c** displayed the superior activity compared to the reference standard drugs (Fig. 3).

Hussain *et al.* [85] reported on novel diazenyl pyrazole moieties and evaluated their anti-inflammatory activity. The derivatives of pyrazole **(15a** and **17c)** displayed the maximum performance, achieving around 80.29% inhibition, comparable to the values of the standard drugs ibuprofen and flurbiprofen (80.38%) (Fig. 4).

Abdellatif *et al*. [86] outlined the synthesis process and investigated the inhibition of cyclooxygenase (COX), assessed potency against inflammation and evaluated the ulcerogenic potential of novel triaryl pyrazoline derivatives, highlighting their promise as selective COX-2 inhibitors. Among the synthesized products, compound **19g** displayed superior proficiency in anti-inflammatory activity compared to all other compounds in the series. Remarkably, the sulfamoyl derivatives (**19i-p**), the fluoro-phenyl derivative (**19j**) and the trimethoxyphenyl derivative (**19o**) exhibited activity values of 73.65% and 65.74%, respectively (Fig. 5). Khloya *et al.* [87] synthesized and conducted a biological evaluation of pyrazolyl thiazole carboxylic acids, exploring their potential as potent anti-inflammatory and antimicrobial agents. Compound **20n** emerged as a highly effective anti-inflammatory representative (Fig. 6) demonstrating the inhibition values ranging from 93.06% to 89.59%. In comparison, the reference standard drug, indomethacin, exhibited an inhibition value of 91.32%.

Abdellatif *et al*. [88] elaborated the synthesis and anti-inflammatory evaluation of newly developed derivatives of triaryl-dihydro-1*H*-pyrazole featuring an aminosulphonyl entity (Fig. 7). Among the investigated compounds (**21a-l**), their anti-

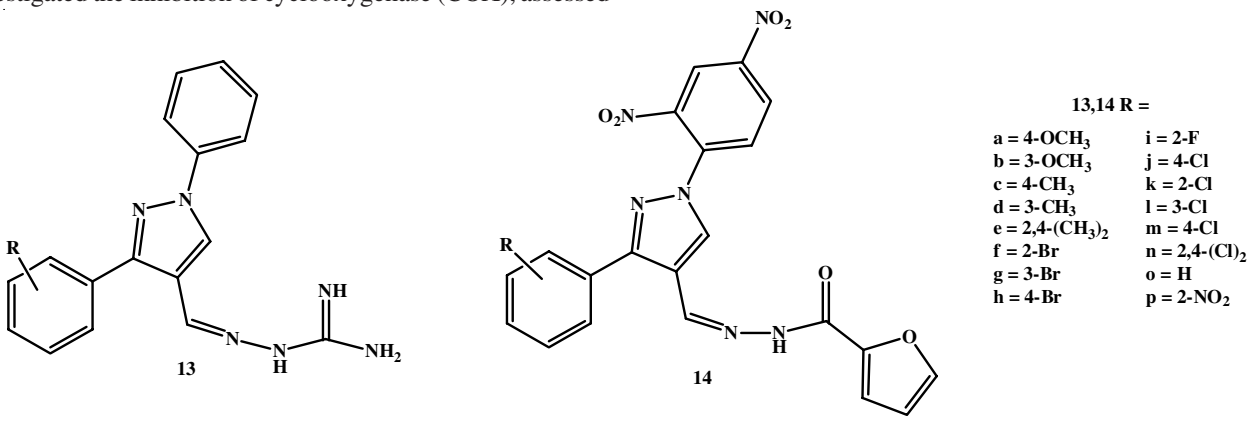


Fig. 3. Chemical structure of 1,3-diaryl pyrazole derivatives

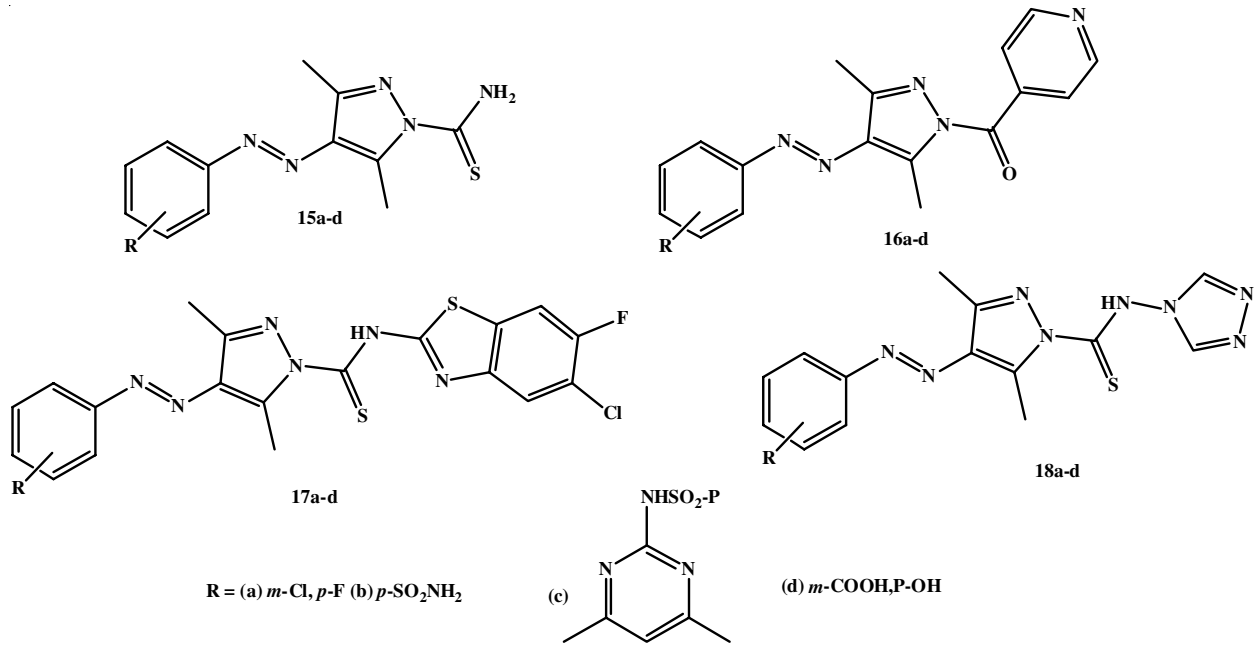
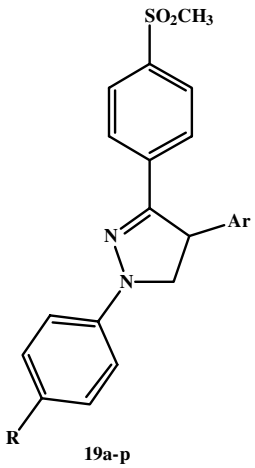
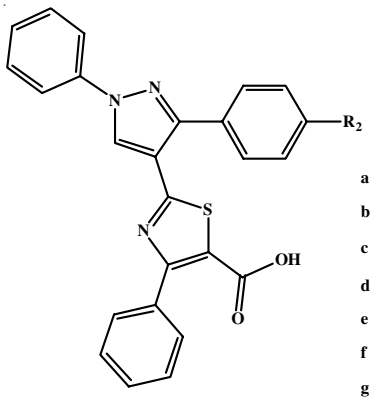


Fig. 4. Chemical structure of pyrazole moieties substituted with diazenyl groups



a, R=COOH, Ar= C_6H_5
b, R=COOH, Ar= 4-FC_6H_5
c, R=COOH, Ar=4-ClC_6H_5
d, R=COOH, Ar= 3-$OCH_3C_6H_4$
e, R=COOH, Ar= 4-$OCH_3C_6H_4$
g, R=COOH, Ar= 3,4-$(OCH_3)_2C_6H_3$
f, R=COOH, Ar=3,4,5-$(OCH_3)_3$ C_6H_2
g, R=COOH, Ar=2-thienyl
i, R=SO_2NH_2, Ar= C_6H_5
j, R=SO_2NH_2, Ar= 4-FC_6H_5
k, R=SO_2NH_2, Ar=4-ClC_6H_5
l, R=SO_2NH_2, Ar= 3-$OCH_3C_6H_4$
m, R=SO_2NH_2, Ar= 4-$OCH_3C_6H_4$
n, R=SO_2NH_2, Ar= 3,4-$(OCH_3)_2C_6H_3$
o, R=SO_2NH_2, Ar=3,4,5-$(OCH_3)_3$ C_6H_2
p, R=SO_2NH_2, Ar=2-thienyl

Fig. 5. Chemical structure of triarylpyrazoline derivatives

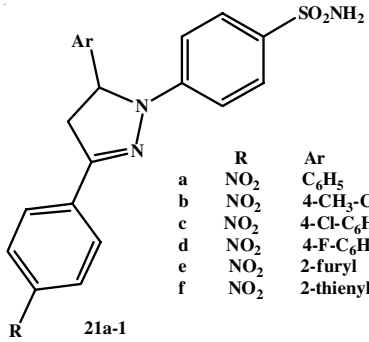


	R_1	R_2		R_1	R_2
a	H	H	i	H	F
b	OCH_3	H	j	OCH_3	F
c	F	H	k	F	F
d	Cl	H	l	Cl	F
e	H	OCH_3	m	H	Cl
f	OCH_3	OCH_3	n	OCH_3	Cl
g	F	OCH_3	o	F	Cl
h	Cl	OCH_3	p	Cl	Cl

Fig. 6. Chemical structure of acidic derivative of pyrazolylthiazole carboxylates

inflammatory action was especially potent, with ED_{50} values of 18, 32, and 36 mg/kg in sequence.

Sribalan *et al.* [89] presented derivatives of 3-(pyridin-4-yl)-1*H*-pyrazole-5-carboxamide chalcone hybrids (Fig. 8) and assessed their anti-inflammatory activity. Among these, compounds (**22a-o**) containing electron-donating substituents such as phenyl, methyl and methoxy (**22b**, **e**, **h**, **k**, **o**) demonstrated improved activity. Conversely, compounds with electron withdrawing groups exhibited similar activity to the parent compound.



	R	Ar		R	Ar
a	NO_2	C_6H_5	g	isobuty	C_6H_5
b	NO_2	4-CH_3-C_6H_5	h	isobuty	4-CH_3-C_6H_5
c	NO_2	4-Cl-C_6H_5	i	isobuty	4-Cl-C_6H_5
d	NO_2	4-F-C_6H_5	j	isobuty	4-F-C_6H_5
e	NO_2	2-furyl	k	isobuty	2-furyl
f	NO_2	2-thienyl	l	isobuty	2-thienyl

Fig. 7. Chemical structure of 2-pyrazoline derivatives

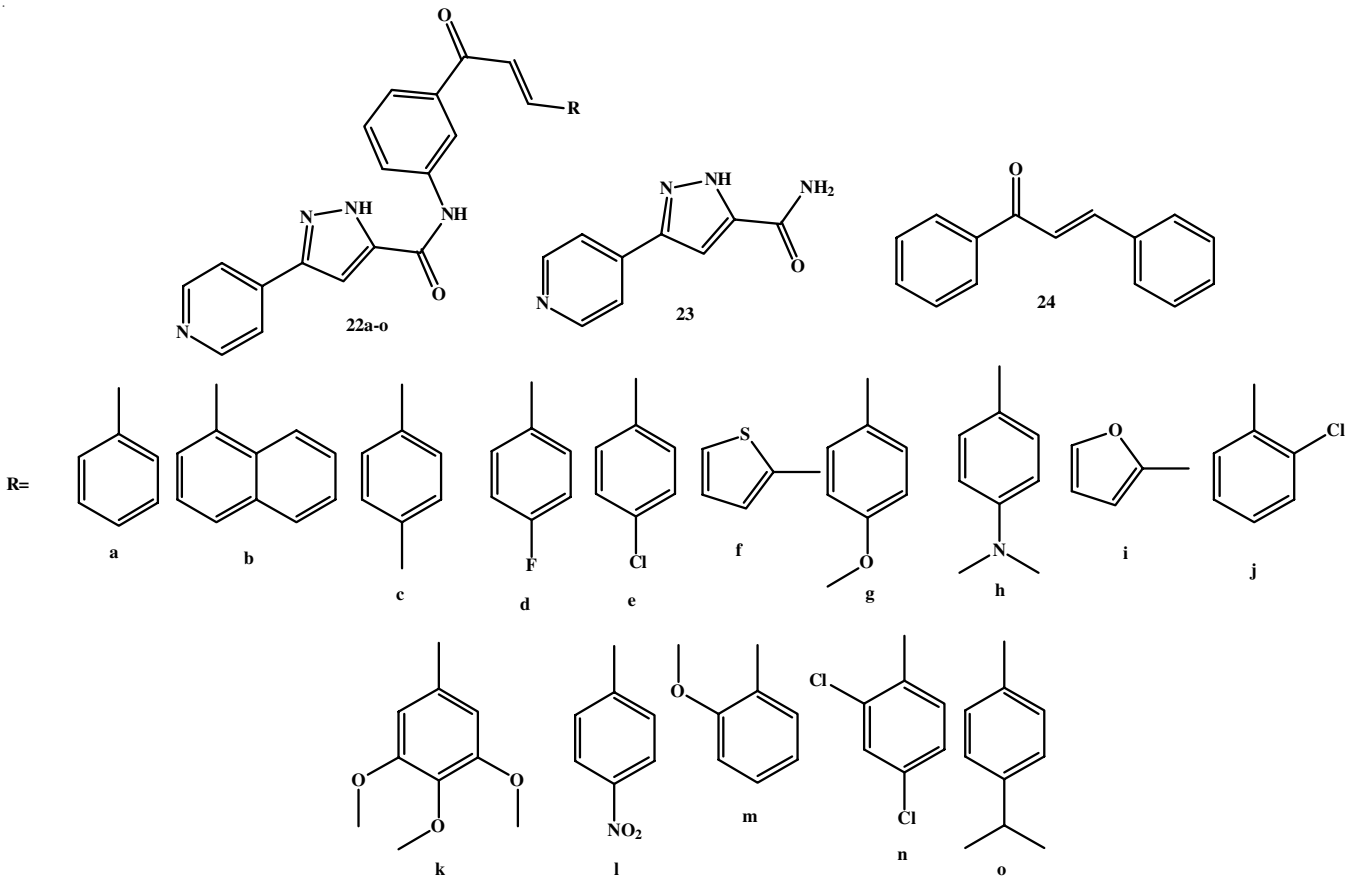


Fig. 8. Chemical structure of 3-(pyridin-4-yl)-1*H*-pyrazole-5-carboxamide chalcones derivatives

Thore *et al.* [90] also synthesized a series of substituted 1*H*-pyrazole-carboxylates derivatives (Fig. 9) and evaluated their anti-inflammatory activity. After 1 h, compound **25a** exhibited an inhibition value of 32.35%, while the standard reference diclofenac sodium showed a value of 36.47%. At 2 h, compounds **25a**, **25c** and **25d** demonstrated inhibition values of 44.48%, 43.96% and 43.62%, respectively. After 3 h, these examined compounds displayed inhibition values ranging from 23.88% to 38.80%.

Chen *et al.* [91] synthesized new anti-inflammatory agents with improved pharmaceutical profiles, specifically derivatives of phenyl-pyrazoline-coumarin. The anti-inflammatory activity of these conclusive derivatives **(26a-m)** was assessed through the carrageenan-induced edema method and by observing pathological changes in rat ankle joints. In terms of edema inhibition, it was observed that the substituents attached to the ring affected the activity. Unexpectedly, derivative **26m**, which contains a flavone moiety, exhibited a significant increase in anti-inflammatory action. In the second method, rats induced with compound **26m** at a dose of 45 mg/kg showed a reduction in inflammatory cell infiltration, bone destruction and synovial hyperplasia (Fig. 10).

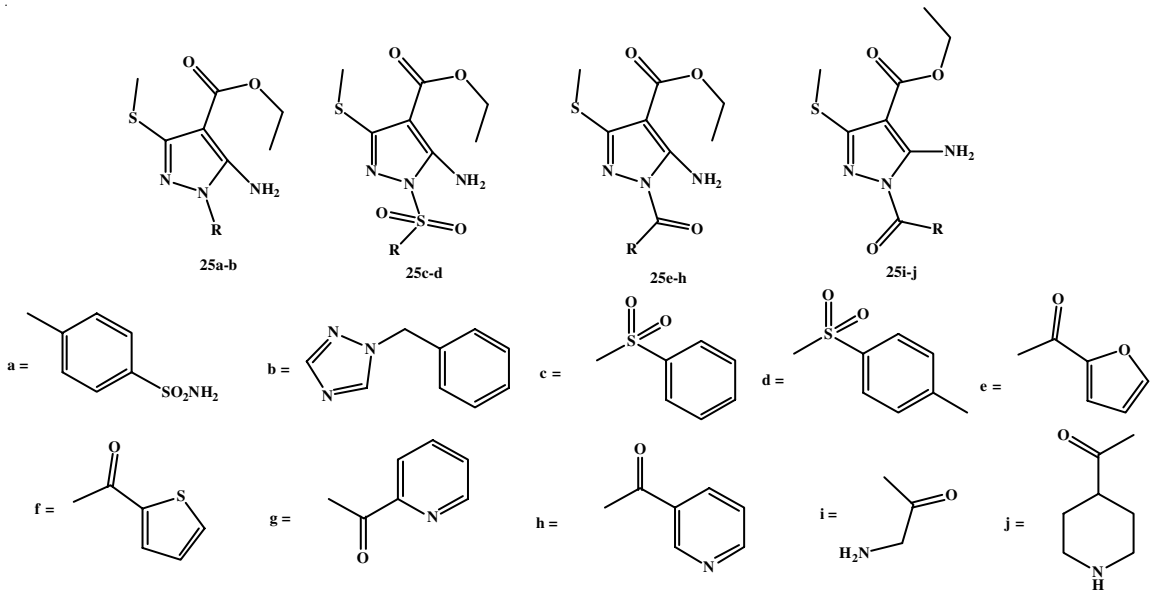


Fig. 9. Chemical structure of 1*H*-pyrazole-carboxylates derivatives

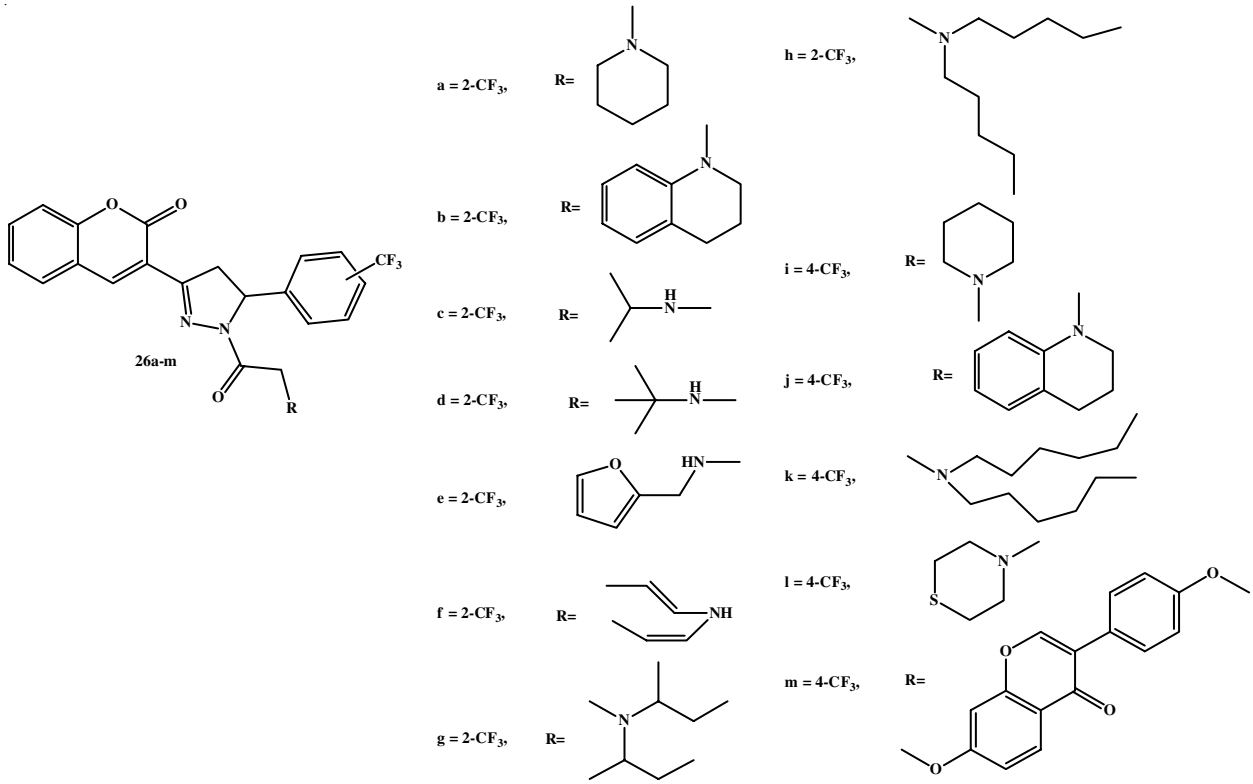


Fig. 10. Chemical structure of aryl pyrazole-coumarins derivatives

Bhat *et al.* [92] introduced a novel series of 3,4,5-trimethoxyphenyl-bearing pyrazole moieties (Fig. 11), exploring their potential anti-inflammatory activity. The synthesized derivatives underwent assessment for their anti-inflammatory action using the LPS-induced iNOS model. Among the compounds **27a-g**, none exhibited inhibition exceeding 51%. Specifically, compounds **27a**, **27d**, **27f** demonstrated inhibition values of 41.8%, 28.2% and 20.3%, respectively. Additionally, derivatives (**27b** and **27g**) decreased the anti-iNOS effect by 2.5-fold, while the activity was heightened by 14% and 12.6% in derivatives (**27c** and **27e**), respectively.

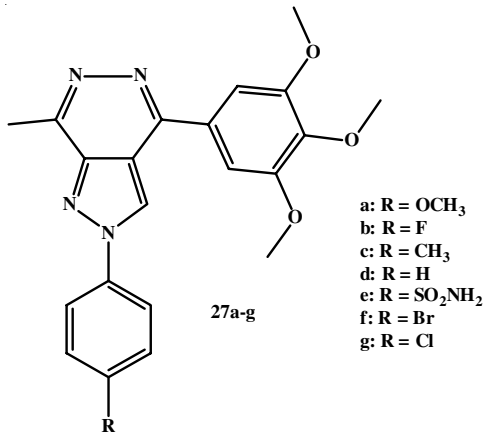


Fig. 11. Chemical structure of pyrazolo[3,4-*d*]pyridazine derivatives

Kumar *et al.* [93] also synthesized a series of novel 5-(1-aryl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-1*H*-tetrazoles and evaluated their inflammatory behaviour on the RAW mouse murine cancer cell line at concentrations of 1, 5 and 10 mg/mL. Among all the compounds, derivatives (**28f** and **28g**) exhibited the most robust anti-inflammatory action compared to the standard reference drug celecoxib. Furthermore, derivatives (**28c**, **28d**, **28f** and **28j**) also inhibited NO production (Fig. 12).

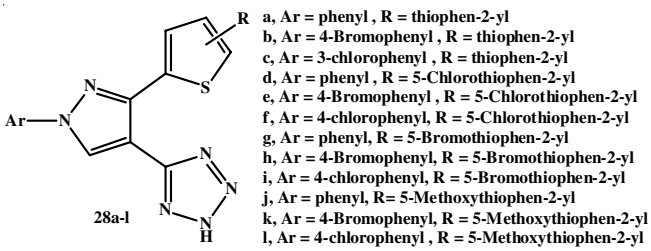


Fig. 12. Chemical structure of 5-(1-aryl-3-(5-substituted-thiophen-2-yl)-1*H*-pyrazol-4-yl)-1*H*-tetrazoles

Kulkarni *et al.* [94] unveiled the green synthesis method for coumarin-pyrazolone hybrids (**29a-l**) (Fig. 13) and evaluated for their anti-inflammatory efficacy. Among these derivatives, namely **29e**, **29f**, **29g**, **29h**, **29i** and **29j**, demonstrated anti-inflammatory actions ranging from 82% to 74%. Notably, derivatives **29c** and **29d** exhibited good activity, while derivatives **29a** and **29b** showed moderate action.

El Shehry *et al.* [95] reported novel pyrazole derivatives and their anti-inflammatory properties. Compounds **30b** and **30d** (Fig. 14) were found to be inactive within the given dosage

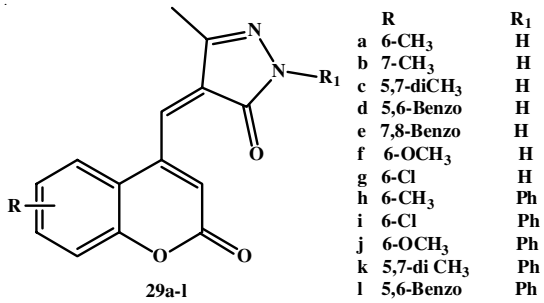


Fig. 13. Chemical structure of 3-methyl-4-((2-oxo-2*H*-chomen-4-yl) methylene)-1-phenyl-1*H*-pyrazol-5-(4*H*)-ones

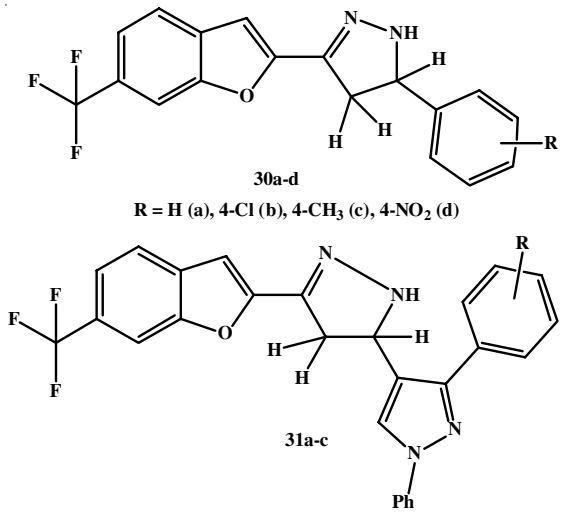


Fig. 14. Chemical structure of synthesized pyrazolines

window of 2 to 4 h. Conversely, derivative **30c** exhibited a decrease in its anti-inflammatory values at different concentrations.

Hassan *et al.* [96] developed novel derivatives of pyrazole (Fig. 15) and investigated their inhibitory potency against inflammation. Compounds **32a**, **33b** and **33e** exhibited inhibition in the range of 13.10 to 22.21. To further explore their anti-inflammatory activity, compounds **32a**, **33b** and **33e** were evaluated using the carrageenan-induced rat paw edema method. Except for derivative **32e**, all other compounds demonstrated higher anti-inflammatory activity compared to the standard reference, celecoxib.

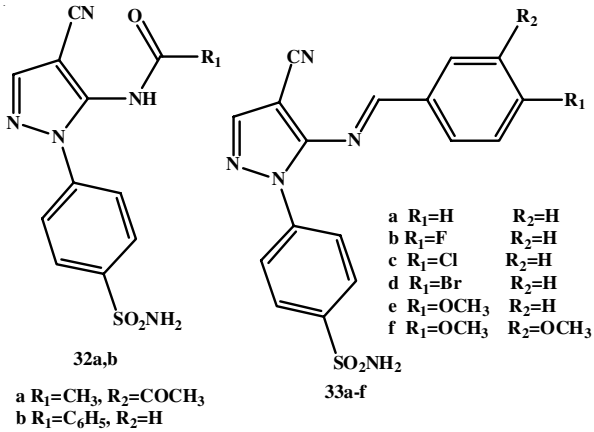
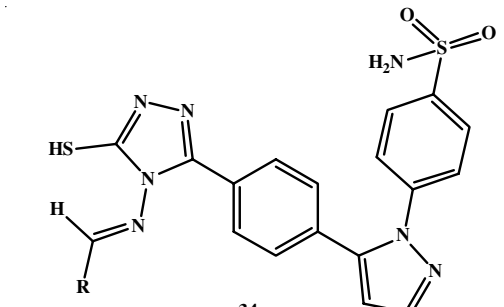


Fig. 15. Chemical structure of substituted pyrazole derivatives

Mustafa *et al.* [97] developed an efficient method for synthesizing novel derivatives, specifically 4-{5-[4-(4-amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)-phenyl]-3-trifluoromethyl-pyrazol-1-yl}benzenesulfonamide (Fig. 16). These derivatives were evaluated for *in vivo* anti-inflammatory activity using the carrageenan-induced method. The results revealed that the majority of derivatives exhibited higher activity compared to the reference standard drug, celecoxib. Particularly, the chlorine-substituted products (**34a**, **34c**, **34d**, **34h**) and the NO_2-substituted product (**34f**) demonstrated pronounced anti-inflammatory properties. Conversely, compounds containing a phenyl ring, bromo and 4-N,N-dimethylaminophenyl groups (**34g**, **34e**, **34m**) showed lower effectiveness in this regard.

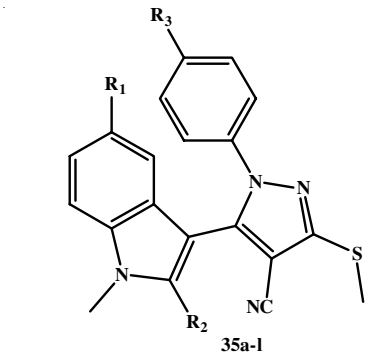


Compd. -R

a: 4-Chlorophenyl	**h: 2-Chlorophenyl**
b: 2,3-Dichorophenyl	**i: 4-Methoxyphenyl**
c: 2,4-Dichorophenyl	**j: 2-Hydroxyphenyl**
d: 3,4-Dichorophenyl	**k: Furfuryl**
e: 4-Bromophenyl	**l: 2-Nitrophenyl**
f: 4-Nitrophenyl	**m: 4-N,N-dimethyl-aminophenyl**
g: Phenyl	

Fig. 16. Chemical structure of 4-{5-[4-(4-amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)-phenyl]-3-trifluoromethyl-pyrazol-1-yl}benzenesulfonamide

Bhale *et al.* [98] synthesized derivatives of tetrasubstituted pyrazole and evaluated their anti-inflammatory potency. The compounds, 1,3,4,5-tetrasubstituted pyrazoles (**35a-l**, Fig. 17), were also assessed for their anti-inflammatory activity using the egg albumin denaturation technique. The derivatives exhibited inhibition activity ranging from 47.23% to 71.08%. Significantly, among all the derivatives, compound **35e** shows notable inhibition at 93.80%. These results were compared with those of the reference drug, diclofenac sodium, which exhibited 90.21% inhibition.



a = R_1=R_2=R_3=H	**g = R_1=Br,R_2=R_3=H**
b = R_1=R_3=H,R_2=CH_3	**h = R_1=OCH_3,R_2=H,R_3=CH_3**
c = R_1=Br,R_2=R_3=H	**i = R_1=R_2=H,R_3=CN**
d = R_1=OCH_3,R_2=R_3=H	**j = R_1=H,R_2=CH_3,R_3=CN**
e = R_1=R_2=H,R_3=CH	**k = R_1=Br,R_2=H,R_3=CN**
f = R_1=H,R_2=R_3=CH_3	**l = R_1=OCH_3,R_2=H,R_3=CN**

Fig. 17. Chemical structure of tetrasubstituted pyrazole derivatives

Kenchappa & Yadav [99] synthesized and evaluated the anti-inflammatory activity of benzofuran pyrazole derivatives (Fig. 18) using the carrageenan-induced paw edema model in rats, with observations made at 3 and 5 h post-dosing. Diclofenac sodium was used as the standard reference drug exhibited the inhibition rates of 82.83% at 3 h and 80.31% at 5 h.

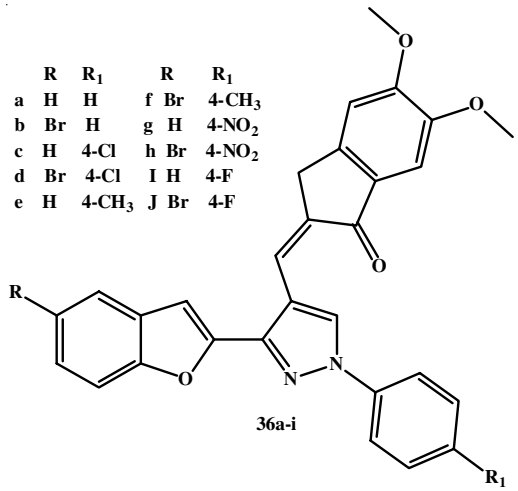
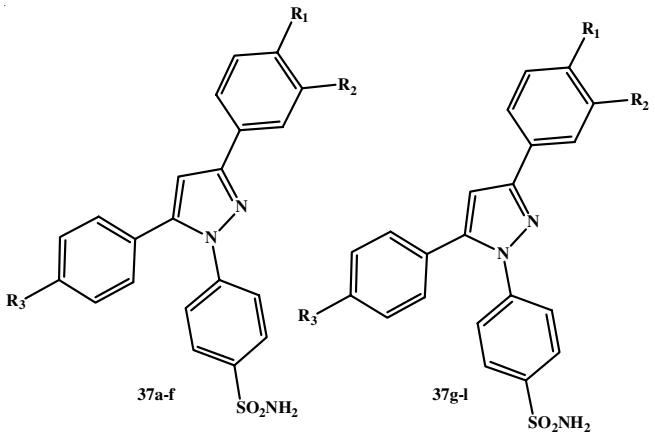


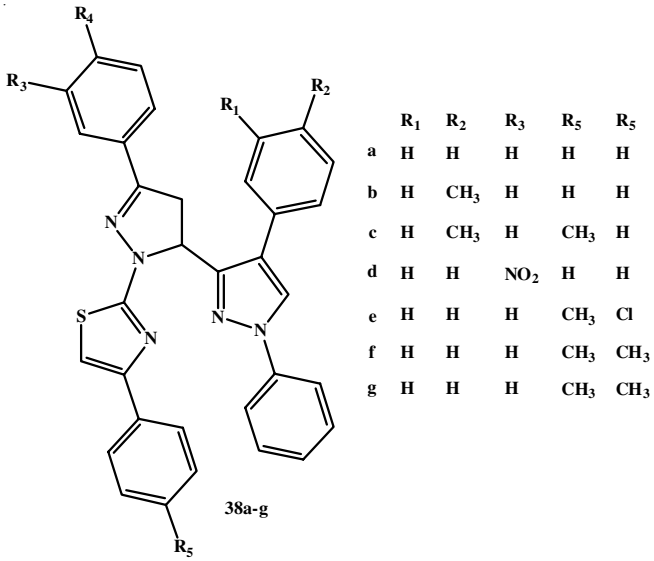
Fig. 18. Chemical structure of new pyrazole derivatives

Abdellatif *et al.* [100] also synthesized new halogenated triarylpyrazoles (Fig. 19) and investigated their anti-inflammatory activity. The inhibition percentages were observed at different time intervals (1 h, 3 h, 6 h) using celecoxib as the standard reference drug in a carrageenan-induced paw edema procedure. Similarly, Raut *et al.* [101] described the synthetic route of asymmetric thiazolyl pyrazolines (Fig. 20) as potential anti-inflammatory agents. Compounds such as **38a**, **38b**, **38c**, **38f**, **38g**, which were substituted with electron donating groups (-CH_3 & -OCH_3), exhibited the best anti-inflammatory properties



a: R_1=OCH_3, R_2=H, R_3=F	**g: R_1=OCH_3, R_2=OCH_3, R_3=F**
b: R_1=OCH_3, R_2=H, R_3=Cl	**h: R_1=OCH_3, R_2=OCH_3, R_3=Cl**
c: R_1=OCH_3, R_2=H, R_3=Br	**i: R_1=OCH_3, R_2=OCH_3, R_3=Br**
d: R_1=OC_2H_5, R_2=H, R_3=F	**j: R_1=SO_2CH_3, R_2=H, R_3=F**
e: R_1=OC_2H_5, R_2=H, R_3=Cl	**k: R_1=SO_2CH_3, R_2=H, R_3=Cl**
f: R_1=OC_2H_5, R_2=H, R_3=Br	**l: R_1=SO_2CH_3, R_2=H, R_3=Br**

Fig. 19. Chemical structure of pyrazole derivatives

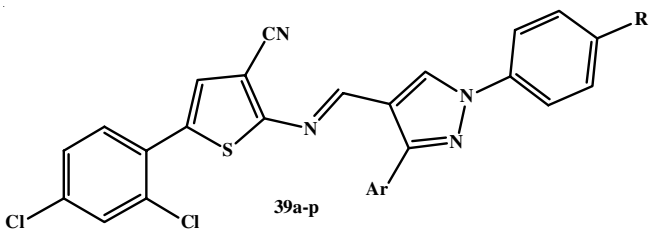


	R_1	R_2	R_3	R_5	R_5
a	H	H	H	H	H
b	H	CH_3	H	H	H
c	H	CH_3	H	CH_3	H
d	H	H	NO_2	H	H
e	H	H	H	CH_3	Cl
f	H	H	H	CH_3	CH_3
g	H	H	H	CH_3	CH_3

Fig. 20. Chemical structure of 1-thiazolyl-2-pyrazolines

with values of 87.1%, 86.23%, 91.74%, 88.07% and 87.15%, respectively. Conversely, compounds substituted with electron-withdrawing groups (-NO_2 and -Cl), namely compound **38d** and **38e**, showed good and lesser properties, with percentages of 72.47% and 36.69%, respectively. These results were compared with diclofenac sodium, which exhibited a value close to 90.21%.

Nayak *et al.* [102] synthesized various pyrazoleclubbed thiophene derivatives (Fig. 21). The synthesized products underwent examination for their anti-inflammatory activity using bovine albumin and protein denaturation assays. Derivatives substituted with halogens exhibited IC_{50} values as follows: **39b** = 34.1 µg/mL, **39d** = 34.3 µg/mL, **39e** = 46.3 µg/mL, **39i** = 40.3 µg/mL and **39m** = 49 µg/mL. The remaining derivatives displayed IC_{50} results in the order: **39a** = 40 µg/mL, **39f** = 41 µg/mL, **39h** = 40.9 µg/mL and **39p** = 42.8 µg/mL. These findings were compared with diclofenac sodium, used as the standard reference, which exhibited an IC_{50} value of 31.4 µg/mL. Kadambar *et al.* [103] conducted the synthesis of pyrazole derivatives using a one-pot three-component azide-alkyne



Ar	R	Ar	R
a = -C_6H_5	4-H	i = C_6H_5	4-Cl
b = 4-Cl-C_6H_4	4-H	j = 4-Cl-C_6H_4	4-Cl
c = 4-F-C_6H_4	4-H	k = 4-F-C_6H_4	4-Cl
d = 4-Br-C_6H_4	4-H	l = 4-Br-C_6H_4	4-Cl
e = 3-Br-C_6H_4	4-H	m = 3-Br-C_6H_4	4-Cl
f = 4-OCH_3-C_6H_4	4-H	n = 4-OCH3-C_6H_4	4-Cl
g = 4-CH_3-C_6H_4	4-H	o = 4-CH_3-C_6H_4	4-Cl
h = 3-Thienyl	4-H	p = 3-Thienyl	4-Cl

Fig. 21. Chemical structure of 2-{[(substituted phenyl-1*H*-pyrazol-4-yl)-methylene]amino}5(2,4dichlorophenyl)thiophene-3-carbonitriles

cycloaddition. Compounds **40a-l** (Fig. 22) examined for their anti-inflammatory properties *via* the denaturation of bovine serum. The IC_{50} values of the derivatives were recorded as follows: **40a** = 51.02, **40b** = 58.71, **40c** = 37.77, **40d** = 28.22, **40e** = 58.97, **40f** = 52.01, **40g** = 211.94, **40h** = 60.54, **40i** = 27.90, **40j** = 28.79, **40k** = 24.33 and **40l** = 57.00 µg/mL. These values were compared with the standard reference diclofenac sodium, which exhibited an IC_{50} value of 22.90 µg/mL.

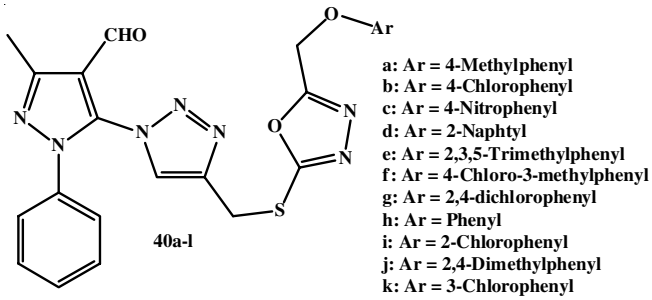


Fig. 22. Chemical structure of 3-methyl-5-(4-(((5-substituted phenoxy-methyl)-1,3,4-oxa-diazol-2-yl)thio)methyl)-1*H*-1,2,3-triazole-1-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde

Bhuvaneswari *et al.* [104] synthesized a new series of derivatives of azo *bis*-antipyrine (Fig. 23) and screened the synthesized compounds for their anti-inflammatory efficacy. Significantly, derivative **41f** demonstrated the highest inhibition at 100 µg/mL, with a percentage of 53%, compared to aspirin, which exhibited 73% inhibition at the same concentration. El-Karim *et al.* [105] designed and synthesized new pyrazole-thiazolidinones (Fig. 24) as potent anti-inflammatories. The derivatives exhibited inhibition percentages as follows: **42q** = 98.16%, **42g** = 96.73%, **42l** = 88.1%, **42b** = 81.5%, **42n** = 76.68%, **42s** = 76.17%, **42o** = 73.82% and **42f** = 71.8%. The standard reference determined the inhibition percentages after 4 h as celecoxib = 73.40%, diclofenac = 73.86% and indomethacin = 96.94%.

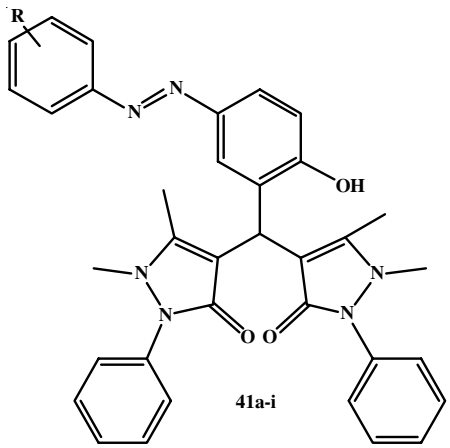


Fig. 23. Chemical structure of azo-bis antipyrine derivatives

Mantzanidou *et al.* [106] synthesized and characterized new derivatives of pyrazoles and pyrazolines. The formed

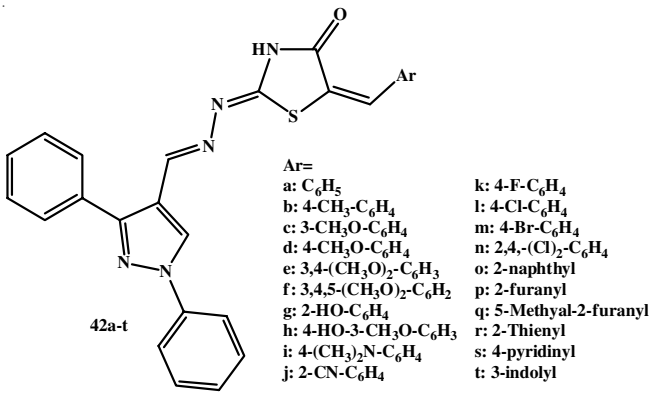


Fig. 24. Chemical structure of pyrazole-methylenehydrazono-thiazolidinones

derivatives (Fig. 25) were assessed for their anti-inflammatory activities using a carrageenan-induced model, with indomethacin serving as the reference standard. The observations revealed percentages of inflammation inhibition as follows: **43b** = 27.0%, **43c** = 38.0%, **43d** = 63.0%, **43e** = 56.0%, **43f** = 30.0%, **43g** = 33.0% and **43h** = 16.0%, whereas the standard drug indomethacin showed 47% inhibition. Based on these findings, it was concluded that derivatives **43d** and **43e** exhibited the most potent anti-inflammatory properties, while derivatives **43b**, **43c**, **43f** and **43g** displayed moderate activity and compound **43a** exhibited no activity. Kumar *et al.* [107] synthesized indole functionalized pyrazoles (**44a-c**) (Fig. 26) and evaluated for their anti-inflammatory properties using a carrageenan induced model. The percentage of inhibition was recorded at various time intervals (0 h, 1 h, 2 h, 4 h) and compared with the standard reference, indomethacin, which exhibited inhibition percentages of 12.12%, 30.30%, 33.34% and 92.59% at 0, 1, 2 and 4 h, respectively. The highest inhibition was

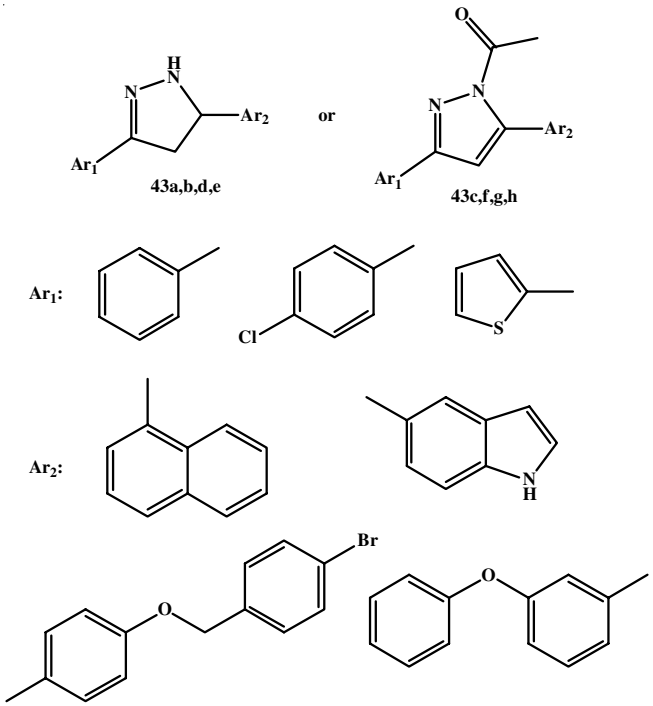


Fig. 25. Chemical structure of pyrazolines and pyrazole derivatives

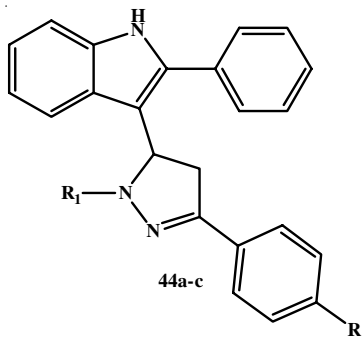


Fig. 26. Chemical structure of indolepyrazoline derivatives

observed after 4 h, with the derivatives ranked as **44a = 44b > 44c** (44.44%, 25.92%). The least inhibition occurred immediately after induction (0 h), with values of 6.06%, 0.0% and 9.09% for **44a**, **44b** and **44c**, respectively. Moderate activity was observed at 1 and 2 h, with percentages of 21.21%, 15.15% and 33.34%, 20%, 23.33% for **44a**, **44b** and **44c**, respectively.

Domiati *et al.* [108] described new amide-linked bipyrazoles (Fig. 27) and evaluated anti-inflammatory effects using an *in vivo* formalin-induced paw edema model. The synthesized compound **45** exhibited remarkable selectivity in *in vitro* cyclooxygenase inhibition assays. Fluoro and methyl group substitutions were found to be the most potent.

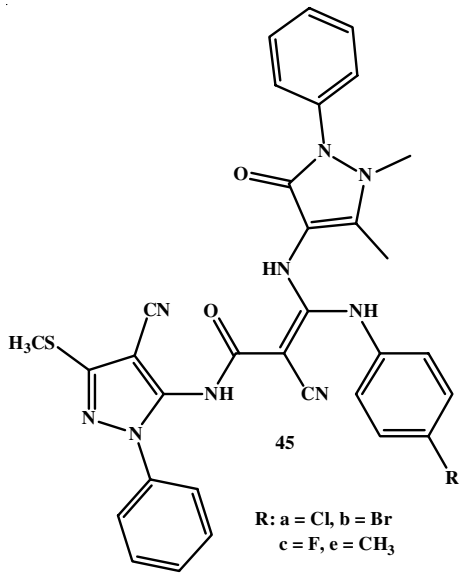


Fig. 27. Chemical structure of 2-cyano-N-(4-cyano3-(methylsulfanyl)-1-phenyl-1*H*-pyrazol-5-yl)-3–(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1*H*-pyrazol-4-ylamino)-3-(substituted amino)acrylamides

Muhammed *et al.* [109] synthesized a novel series of (2*E*)-3-(4-methylphenyl)-1-phenylprop-2-en-1-onesand evaluated their *in vivo* inhibitory potential against inflammation using the carrageenan-induced paw edema methodology. Compounds **46a**, **46h**, **46j** and **46l** (Fig. 28) exhibited significant activity, while compounds **46g** and **46k** demonstrated moderate anti-inflammatory effects compared to celecoxib. Similarly, Gudimani *et al.* [110] developed an innovative methodology for synthesizing derivatives of trisubstituted pyrazole propionic acid, subsequently assessing their anti-inflammatory efficacy. The

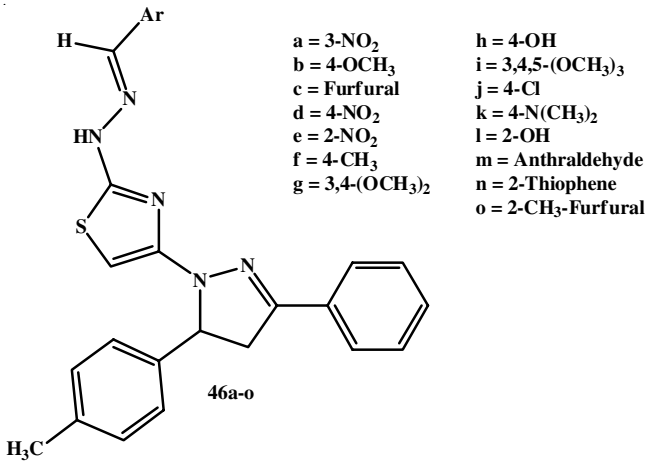


Fig. 28. Chemical structure of (2*E*)-3-(4-methylphenyl)-1-phenylprop-2-en-1-ones derivatives

newly synthesized pyrazole acid derivatives **(47a-f)** and pyrazole ester derivatives **(48a-f)** underwent screening for their anti-inflammatory activity against matrix metalloproteinases (MMPs), specifically MMP-2 and MMP-9, utilizing the gelatin zymography method. Compounds **47a**, **47b**, **47c**, **47d**, **47e** and **47f** (Fig. 29) exhibited a significant activity against MMP-2, demonstrating inhibition rates of 88%, 86%, 80%, 83%, 85% and 79%, respectively. Compounds **48a**, **48b**, **48c** and **48f** showed moderate activity against MMP-2, with inhibition rates of 68%, 66%, 70% and 77%, respectively.

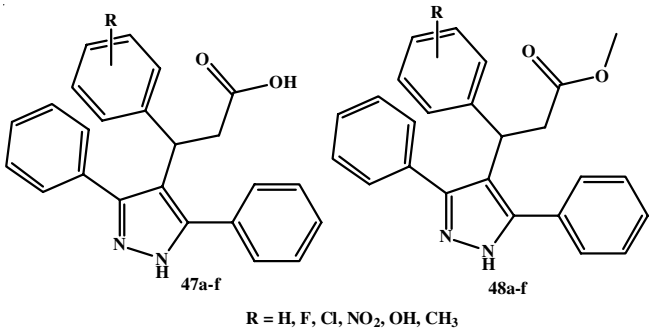


Fig. 29. Chemical structure of 3-(3,5-diphenyl-1*H*-pyrazol-4-yl)-3-(aryl)propanoic acid **46(a-f)** and propanoate **47(a-f)** derivatives

Ahmed *et al.* [111] synthesized a series of novel derivatives of pyrazole-chalcones and assessed their anti-inflammatory activity. In the *in vitro* cyclooxygenase (COX) inhibition assay, the inhibitory potential of highly potent pyrazole/chalcone hybrids, specifically **49f**, **49g**, **50f** and **50g** (Fig. 30) against both bovine COX-1 and COX-2 enzymes, was evaluated. Similarly, Fadaly *et al.* [112] also synthesized pyrazole derivatives incorporating oxime and nitrate moieties and conducted an evaluation of their anti-inflammatory activity. The assessment of the compounds' COX-1/COX-2 inhibition involved the use of the COX-1 inhibitor screening Kit-K548 and COX-2 inhibitor screening Kit-K547 (Biovision, Milpitas, CA) for isozyme-specific monitoring. The results revealed that compounds **51c**, **51d**, **51e**, **52a**, **52b**, **52c**, **52e** and **52f** (Fig. 31) exhibited substantial inhibitory activities against the COX-1 isozyme, with IC_{50} values ranging from 5.18 to 8.18 μM. Conversely,

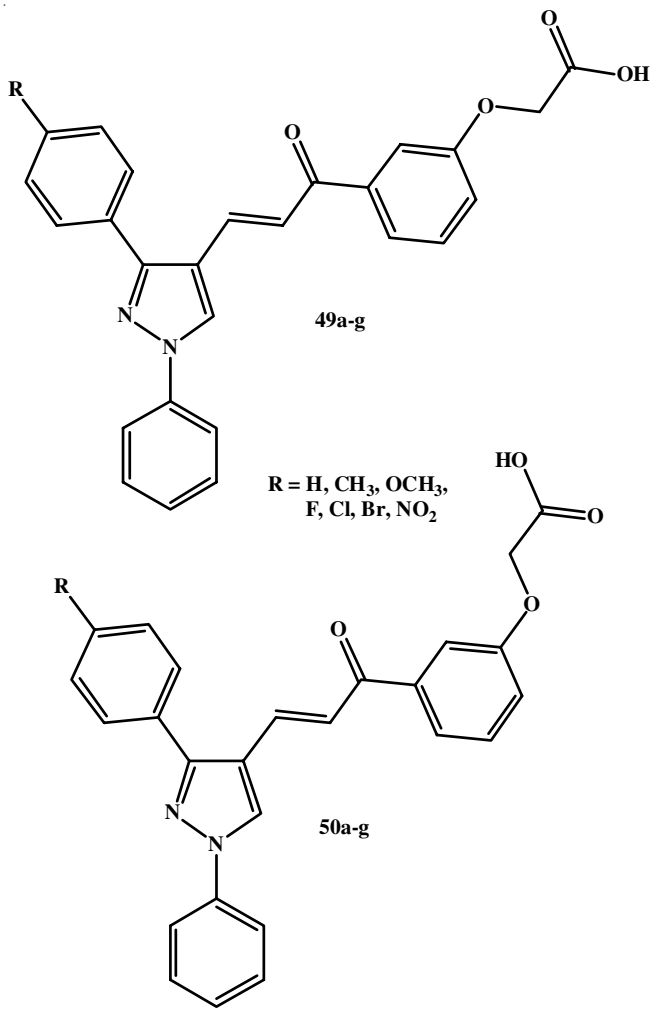


Fig. 30. Chemical structure of pyrazole-chalcone derivatives

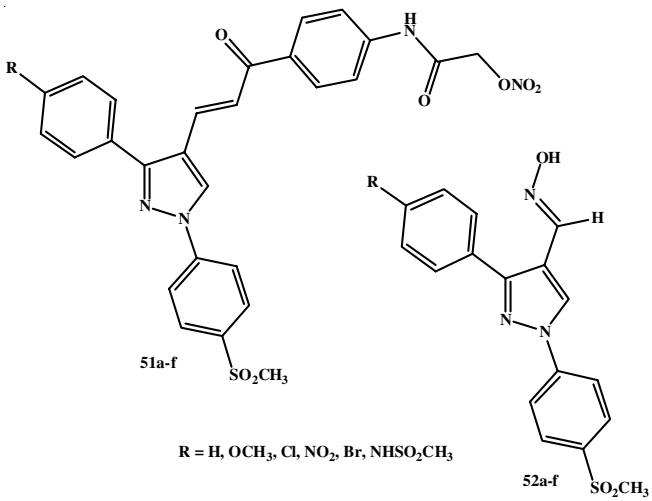


Fig. 31. Chemical structure of pyrazole derivatives incorporating oxime and nitrate moieties

compounds **51b**, **51c**, **51e**, **52a** and **52e** demonstrated a significant inhibitory activities against the COX-2 isozyme, with IC_{50} values ranging from 0.20 to 0.39 μM.

Challenges and limitations of pyrazoles as anti-inflammatory drug: While pyrazoles show promise as potential anti-

inflammatory agents, they are not without challenges and limitations. One notable concern is their potential for toxicity, especially with prolonged or high-dose usage. Ensuring the safety profile of pyrazole derivatives, including their impact on vital organs such as the liver and kidneys, is crucial. Another challenge is achieving selectivity, as it remains difficult to specifically target inflammatory pathways without interfering with vital physiological functions. Careful design strategies are necessary to minimize off-target effects. Additionally, certain pyrazole derivatives undergo metabolic changes that may compromise their effectiveness, highlighting the importance of metabolic stability and bioavailability. A continuing area of study involves optimizing pharmacokinetic properties to deliver long-lasting therapeutic benefits. The development of patient-friendly formulations of pyrazoles may be necessary due to the limited available routes of administration, which could impact their clinical utility.

The discovery of pyrazole derivatives that effectively target multiple pathways is complicated by the variability of inflammatory diseases, each with distinct molecular processes. Challenges include the scarcity of clinical investigations, necessitating further research to validate preclinical findings. Market expansion and accessibility may be hindered by cost-related issues and regulatory hurdles. Achieving high target specificity and managing potential drug interactions are also critical considerations. Despite these challenges, ongoing research and collaborative efforts are aimed at overcoming these limitations and unlocking the full therapeutic potential of pyrazoles in anti-inflammatory applications.

Future perspectives: Pyrazoles hold significant promise as anti-inflammatory medications, with numerous ongoing research initiatives aimed at addressing current challenges. A critical focus area is enhancing the design of pyrazole derivatives to achieve greater target selectivity. The quest for drugs that specifically modulate particular inflammatory pathways while minimizing off-target effects is expected to be guided by advancements in molecular modeling and structure-activity relationship investigations. The trajectory of pyrazole-based anti-inflammatory drug development appears promising, particularly in the realm of personalized medicine. In addition, combination therapy is a potential path that should be investigated. Exploring potential interactions between pyrazoles and other anti-inflammatory drugs could enhance effectiveness while mitigating adverse effects. Combinatorial approaches have the potential to revolutionize the treatment landscape for inflammatory diseases, paving the way for more refinement and efficacious therapeutic strategies. Ultimately, the prospects of pyrazoles as anti-inflammatory medications hinge on the collaboration among academic institutions, the pharmaceutical industry and regulatory agencies.

Conclusion

This study encompasses essential insights into the synthesis and anti-inflammatory properties of multiple pyrazole analogues. Given the heightened pharmacological efficacy associated with pyrazole derivatives, their design and synthesis represent a captivating realm of research. While pyrazoles have been recognized for decades, this study significantly contributes by shedding light on the anti-inflammatory properties inherent in the pyrazole scaffold. The array of examples examined in this study underscores the innate capability of pyrazoles in combating inflammation and the development of various related systems, reflecting their evolving biological behaviours. Research indicates that introducing electron-withdrawing or electron-releasing groups, as well as integrating heterocyclic rings onto pyrazoles, induces alterations in the inhibition percentage against inflammation. This review aims to help researchers in pinpointing gaps in the exploration of pyrazole derivatives and streamlining the synthesis of novel pyrazole systems with anti-inflammatory potential. The objective is to pave the way for the swift application of pyrazole derivatives across diverse domains.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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