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THERAPEUTIC POTENTIAL OF PYRAZOLE CONTAINING COMPOUNDS: AN UPDATED REVIEW

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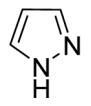
Among a large number of nitrogen-containing heterocyclic compounds, pyrazole is a privileged scaffold with the molecular formula $C_3H_3N_2H$. It consists of a five-membered ring with 3-carbon atoms and 2-nitrogen atoms which are present in adjacent positions. The nucleus has attracted synthetic interest due to numerous pharmacological activities. This molecule is used as one of the basic moieties for leads in the area of drug discovery and development and thereby plays a vital role in the field of medicinal chemistry. The present review article highlights the SAR studies of potent compounds of pyrazole and its derivatives (2015–2022) reported as anti-inflammatory, anticancer, antidiabetic, anticonvulsant, antimicrobial, antimycobacterial, antineurodegenerative and antioxidant. Furthermore, a patent application published in this period is also discussed. Google, PubMed, Cochrane, Scopus, ResearchGate, Google Scholar, and Science Direct were primarily used for article search, whereas the databases used for the pyrazole patent were Espacenet, Google Patent, and SciFinder. More than one hundred thirty papers were screened after which inclusion and exclusion criteria were applied to make this review article. We hope the current review article can pave the way for the future drug design and development of pyrazole derivatives as a potential drug candidate.

Keywords: pyrazole; heterocyclic compound; pharmacological activity; drug discovery; medicinal chemistry; anti-inflammatory.

INTRODUCTION

Heterocyclics are a unique class of compounds. The heterocyclic scaffolds are getting special recognition as they belong to the family of molecules with established medicinal chemistry applications [1]. There are many biologically active molecules composed of five-membered rings with two hetero atoms of which one of them, is a pyrazole ring. Pyrazole **(1)** (Fig. 1) is a privileged heterocyclic compound. It is a widely used pharmacophore nucleus due to its multiple pharmaceutical applications, has the chemical formula $C_3H_3N_2H$ and consists of a five-membered ring with 3-carbon atoms and 2-nitrogen atoms which are present in adjacent positions [2]. The pyrazole word was coined by the German chemist Ludwig Knorr in the year 1883. Its derivatives have a broad range of biological activities—for example anti-inflammatory, anticancer, antidiabetic, anticonvulsant, antimicrobial, antimycobacterial, antineurodegenerative, and antioxidant [3 – 5]. The other synonyms are 1,2-diazole, 1*H*-pyrazole, and 1*H*-pyrazole. Moreover, 1*H*-pyrazole is also known as the 1*H*-tautomer of pyrazole and is a conjugate base of pyrazoline and a conjugate acid of pyrazol-1-ide. It is also a tautomer of 3*H*-pyrazole and 4*H*-pyrazole.

Several pyrazole derivatives have been used for a long time in medicines such as zaleplon **(2)**, celecoxib **(3)**, and betazole **(4)**. Additionally, its derivatives are also widely used as herbicides, insecticides, and fungicides such as tebufenpyrad **(5)**, fenpyroximate **(6)**, fipronil **(7)**, and tolfenpyrad **(8)** (Fig. 2) [6, 7]. Heterocycles containing pyrazole rings are also of major interest due to their synthetic usefulness as synthetic reagents in guanylating agents, chiral auxiliaries, and multicomponent systems. Various natural products with pyrazole rings that have pharmacological, physiological, and toxicological properties have been well



(1)

Fig. 1. Chemical structure of pyrazole.

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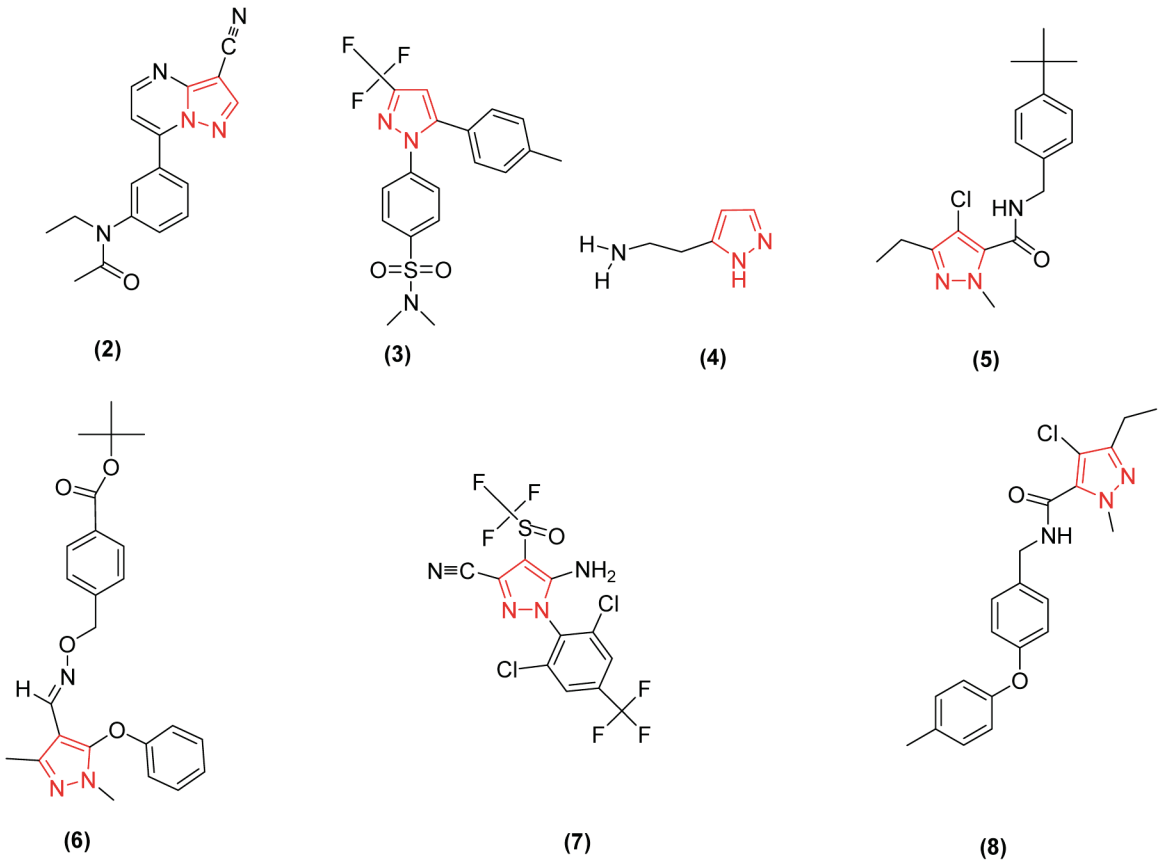


Fig. 2. Marketed drugs containing pyrazole scaffold: zaleplon **(2)**, celecoxib **(3)**, betazole **(4),** tebufenpyrad **(5)**, fenpyroximate **(6)**, fipronil **(7)** and tolfenpyrad **(8)**.

known for a long time. Furthermore, it is also reported that various substituted pyrazole derivatives are used as extraction reagents and chelation for many metal ions [8 – 11].

Due to the importance of pyrazole derivatives in numerous areas, especially in medicinal chemistry, the current review paper focuses on the biological significance of diverse pyrazole derivatives. The present review article highlights the SAR studies of potent compounds of pyrazole and its derivatives (2015–2022) reported as anti-inflammatory, anticancer, antidiabetic, anticonvulsant, antimicrobial, antimycobacterial, antineurodegenerative and antioxidant. Furthermore, patent applications published in this period are also discussed. We hope the current review article can pave the way for the future drug design and development of pyrazole derivatives as a potential drug candidate. The present survey highlights a wide perspective regarding the biological significance of pyrazole and its derivatives (Table 1).

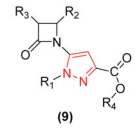
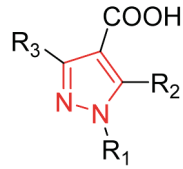
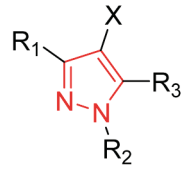
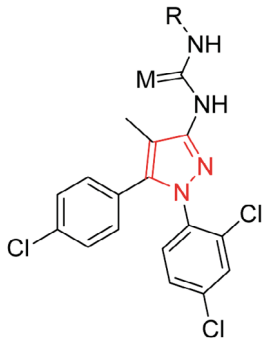
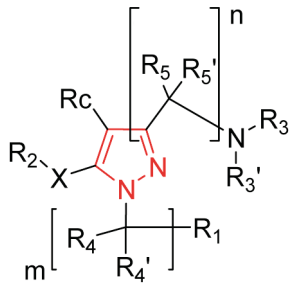
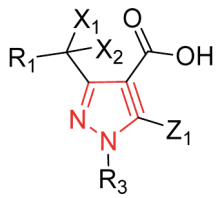
SEARCH STRATEGY

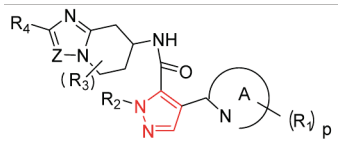
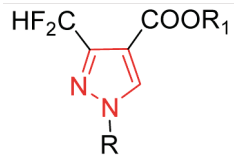
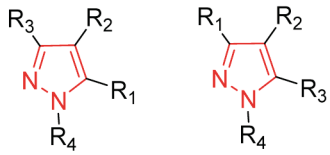
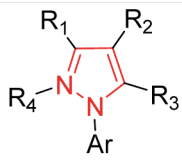
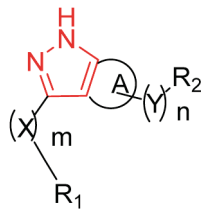
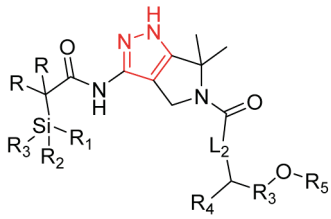
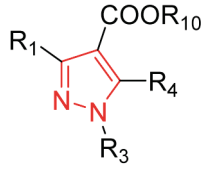
We performed an electronic search to compile existing literature related to the pyrazole nucleus. Different search engines were used such as Google, PubMed, Cochrane, Scopus, Research Gate, Google Scholar, and Science Direct to find out already existing literature on this nucleus. Apart from that, the databases used for the information related to the pyrazole patent are Espacenet, Google Patent, and SciFinder. More than one hundred thirty papers were screened and then inclusion and exclusion criteria were applied to make this review article. The key terms used during the electronic search were “pyrazole”, “pyrazole derivatives”, and “therapeutic activity of pyrazole nucleus”. It took eight months to compile data for the preparation of this article.

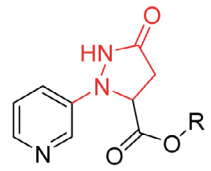
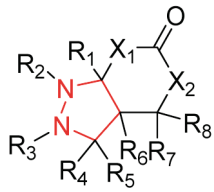
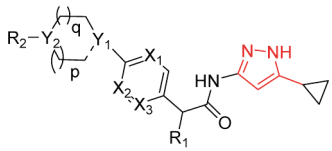
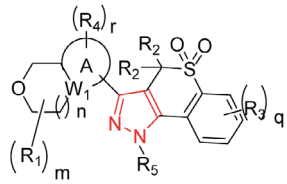
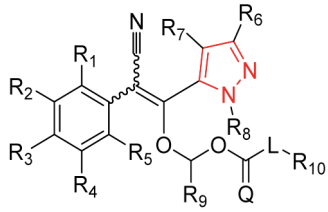
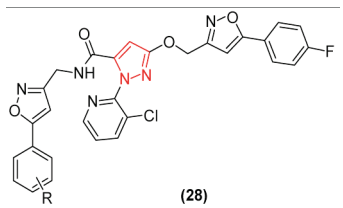
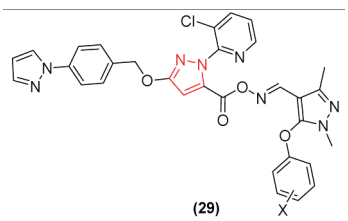
BIOLOGICAL SIGNIFICANCE

The pyrazole ring is one of the leading structural motifs found in various pharmacologically active compounds. Several biologically or pharmacologically active compounds are obtained from this moiety by placing different substituents at various places. From the literature survey, it is concluded that the derivatization of pyrazole is done for pharmacological properties.

TABLE 1. Patent filed for pyrazole derivatives (2015–2022)

S. No.	Patent Application number	Year of filing	Applicant name	Patent office	Compound	Referenc esces
1.	201810399628.1	2018	South-Central University For Nationalities	China	 (9)	[12]
2.	US20160244412A1	2016	SRF Limited, Gurgaon (IN)	United States	 **(10)**	[13]
3.	WO2016158716A1	2016	Asahi Glass Co., Ltd.	International	 **(11)**	[14]
4.	WO2016184310A1	2016	Institute of Toxic Drugs, Academy of Military Medical Sciences, Chinese People's Liberation Army	International	 **(12)**	[15]
5.	WO2018001973A1	2018	Laboratorios Del Dr. Esteve, S.A.	International	 **(13)**	[16]
6.	WO2016152886A1	2016	Asahi Glass Co Ltd.	International	 **(14)**	[17]

S. No.	Patent Application number	Year of filing	Applicant name	Patent office	Compound	Referenc esces
7.	US9777000B2	2016	Mochida Pharmaceutical Co Ltd	United states	 **(15)**	[18]
8.	WO2015155713A1	2015	Isagro S.P.A	International	 **(16)**	[19]
9.	WO2015155680A3	2015	Bayer CropScience AG	United States	 **(17)** **(18)**	[20]
10.	WO2015155680A3	2015	Institut Pasteur	International	 **(19)**	[21]
11.	US10294207B2	2015	Green cross corporation Korea	United States	 **(20)**	[22]
12.	WO2017188357A1	2017	Ube Industries, Ltd.	International	 **(21)**	[23]
13.	WO2017129759A1	2017	Solvay Sa	International	 **(22)**	[24]

S. No.	Patent Application number	Year of filing	Applicant name	Patent office	Compound	Referencesces
14.	US9522900B2	2015	Dow AgroSciences, LLC.	United states	 **(23)**	[25]
15.	WO2017196982A1	2017	Georgia State University Research Foundation, Aviragen Therapeutics, Inc.	International	 **(24)**	[26]
16.	2019247885	2019	Aurigene Discovery Technologies Limited	Australia	 **(25)**	[27]
17.	113754685	2021	Jiangsu Hengrui Medicine Co., Ltd.Jiangsu Hengrui Pharmaceutical Co., Ltd. Shanghai Hengrui Pharmaceutical Co., Ltd.Shanghai Hengrui Pharmaceutical Co., Ltd.	China	 **(26)**	[28]
18.	US11104648B2	2021	Zhejiang Res Institute of Chemical Industry Co Ltd [Cn]; Sinochem Lantian Co Ltd [Cn]	United states	 **(27)**	[29]
19.	CN111303140A	2020	Univ Nantong	China	 **(28)**	[30]
20.	CN111518079A	2020	Univ Nantong	China	 **(29)**	[31]

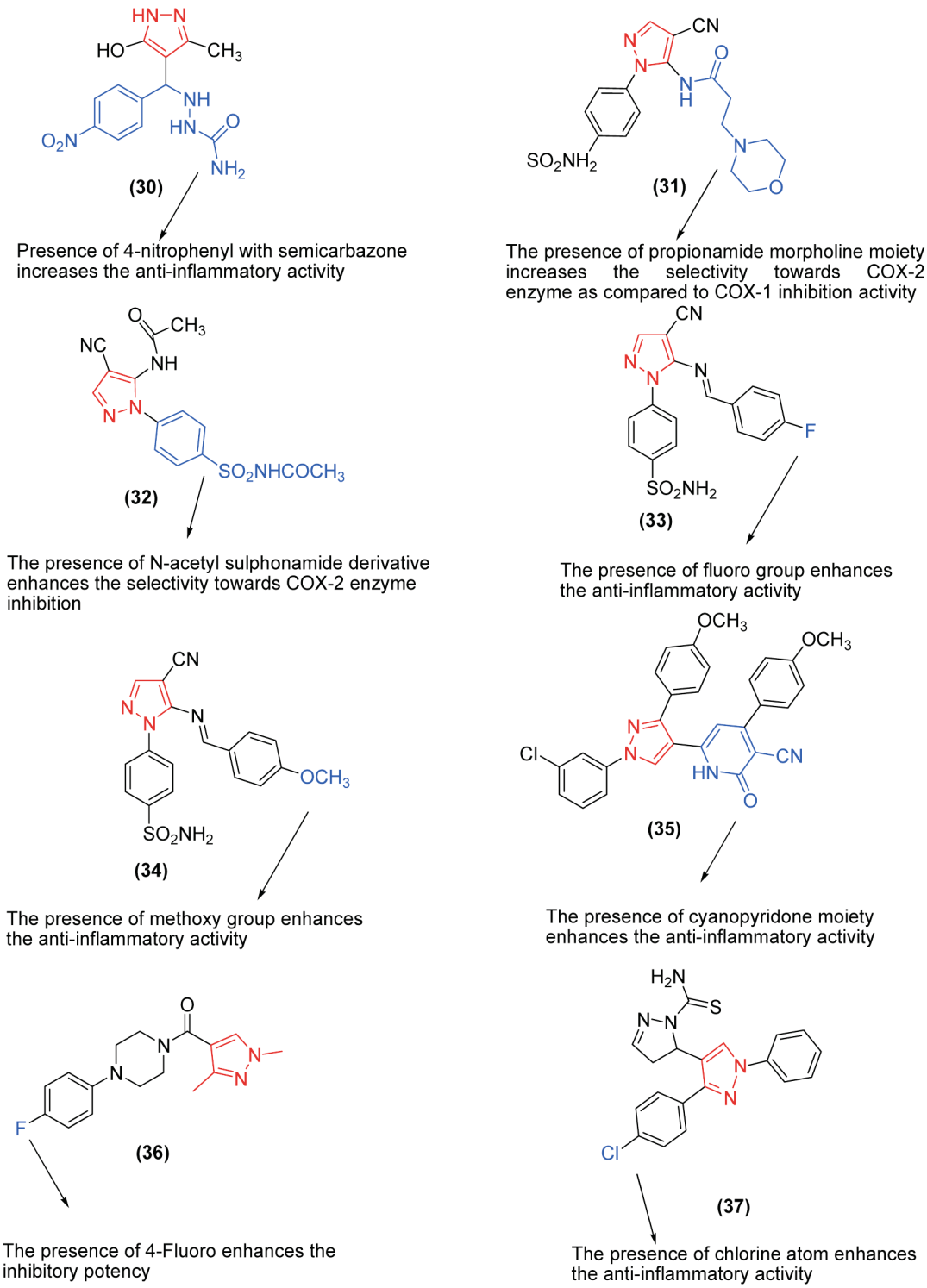


Fig. 3. Chemical structures and SAR studies of reported potent pyrazole derivatives with anti-inflammatory activity **(30 – 37)**.

Pyrazole derivatives with anti-inflammatory activity (Fig. 3)

Kumar, et al. reported a novel series of pyrazole derivatives. The derivatives were synthesized from the condensation technique by using ultrasound irradiation. In this whole series, compound **(30)** was observed as a most potent compound with better activity against the anti-inflammatory drug diclofenac sodium. The SAR studies indicated that the presence of 4-nitrophenyl along with the semicarbaone moiety increases anti-inflammatory activity [32].

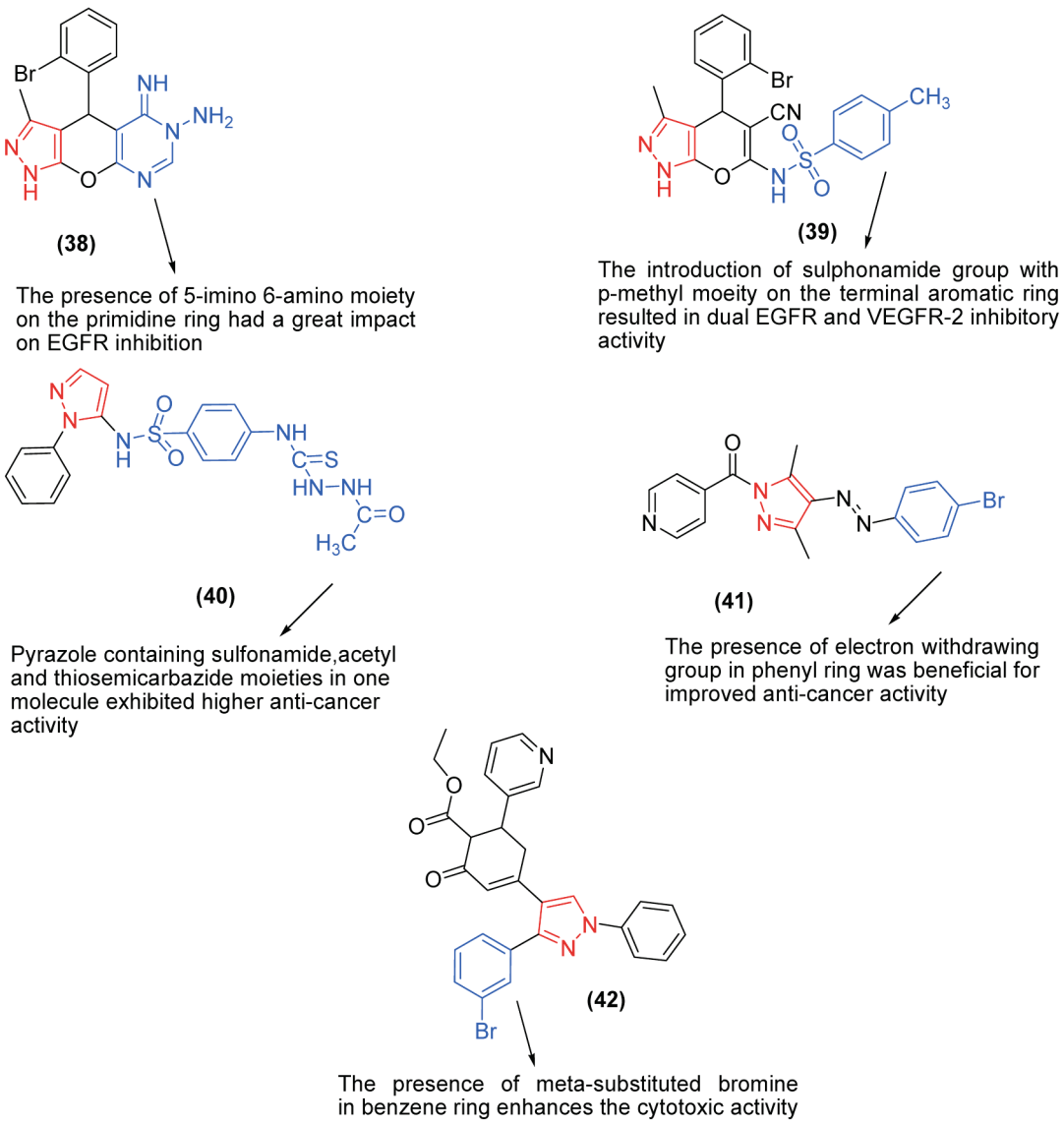


Fig. 4. Chemical structures and SAR studies of potent pyrazole derivatives with anticancer activity **(38 – 42)**.

Hassan, et al. designed, synthesized, and evaluated a novel series of pyrazole derivatives. The synthesized derivatives were biologically evaluated for COX-1 and COX-2 inhibitory activity. In this series, compound **(31-34)** was found to exhibit good activity for the COX-2 enzyme. The SAR studies indicated that the presence of propionamide morpholine moiety **(31)** increases the selectivity towards COX-2 enzyme in comparison to COX-1 inhibition activity. For compound **(32)**, the presence of the *N*-acetyl sulphonamide derivative enhances the selectivity towards COX-2 enzyme inhibition. For compound **(33)**, the presence of the fluoro group enhances the anti-inflammatory activity (IC_{50} = 38.73 nM) and for compound **(34)**, the presence of methoxy group enhances the anti-inflammatory activity (IC_{50} = 39.14 nM) [33].

Nossier, et al. developed some novel pyrazole-substituted derivatives and evaluated the derivatives for anti-inflammatory activity. Among the entire synthesized derivatives, compound **(35)** displayed increased potency. The SAR studies indicated that the presence of cyano pyridone moiety enhances anti-inflammatory activity and displayed 89.57% inhibition of edema than the reference standards celecoxib and indomethacin [34].

Masih, et al. reported some novel pyrazole derivatives. The synthesized derivatives were biologically evaluated for anti-inflammatory activity. Among all the synthesized derivatives, compound **(36)** was found as the most potent compound in this series. The SAR studies confirmed that the presence of the fluoro group in the 4-position enhances inhibitory potency. This finding suggests that this compound

may be used as a lead for further discovery of a more potent anti-inflammatory agent [35].

Yan, et al. synthesized 18 novel pyrazole derivatives. All the synthesized derivatives were biologically screened for anti-inflammatory activity. Among the entire synthesized derivatives, compound **(37)** showed 66.4% inhibition for LPS-induced TNF-á release and treating xylene-induced ear edema. The SAR studies indicated that the presence of chlorine atoms enhances anti-inflammatory activity. The reported anti-inflammatory activity trend was $Cl > H > CH_3$ [36]

Pyrazole derivatives with anticancer activity (Fig. 4)

Saleh, et al. reported some novel pyrazole derivatives for the treatment of cancer. Among all the synthesized derivatives, compounds **(38)** with $IC_{50} = 0.06$ μM and **(39)** with $IC_{50} = 0.22$ μM were identified as potent EGFR and VEGFR-2 inhibitors. The SAR studies of compound **(38)** indicated that the presence of 5-imino-6-amino moiety on the pyrazole ring had a great impact on EGFR inhibition, whereas in compound **(39)**, the addition of the sulphonamide group with p-methyl group on the terminal aromatic ring was responsible for dual EGFR and VEGFR-2 inhibitory activity [37].

El-Gaby, et al. designed, synthesized, characterized, and biologically screened a novel series of pyrazole derivatives as anticancer agents. Of this whole series, compound **(40)** with $IC_{50} = 2.14$ μg/ml showed better activity in comparison to the reference drug doxorubicin with $IC_{50} = 43.6$ μg/ml. The SAR studies indicated that the presence of sulfonamide, acetyl, and thiosemicarbazide moieties in the pyrazole molecule showed improved anticancer activity [38].

Alsayari, et al. reported some novel pyrazole derivatives for the treatment of colon cancer. In this series, compound **(41)** was found to be the most promising candidate against colorectal carcinoma cell lines with $IC_{50} = 4.2$ μM acting through xanthine oxidase inhibition with $IC_{50} = 0.83$ μM. The anticancer activities of pyrazolyl derivatives might be due to xanthine oxidase inhibition. The SAR studies revealed that the presence of an electron withdrawing group attached to the phenyl ring was beneficial for anticancer activity [39].

Alam, et al. reported a novel series of pyrazole derivatives. The synthesized compounds were biologically evaluated for the inhibition of topoisomerase IIα activity and *in-vitro* for cytotoxicity studies against normal and cancerous cell lines. Among all the synthesized analogs, compound **(42)** was observed to have the highest cytotoxicity for HeLa ($IC_{50} = 7.01 \pm 0.60$ μM), NCI-H460 ($IC_{50} = 8.55 \pm 0.35$ μM), and MCF-7 ($IC_{50} = 14.31 \pm 0.90$) cell lines. The SAR studies indicated that the presence of a *meta*-substituted bromine group in benzene moiety enhances cytotoxic activity. In compounds with the *m*-substituted electron-withdrawing group, the cytotoxic order for cancerous cell lines was $Br > NO_2$ [40].

Pyrazole derivatives with antidiabetic activity (Fig. 5)

Bansal, et al. investigated fourteen new thiazolidine-2, 4-dione derivatives coupled with pyrazole moiety. The synthesis was performed in four steps. The new compounds were biologically screened for antidiabetic, antioxidant, and anti-inflammatory activity. In this series, compound **(43)** was found to have blood glucose-lowering properties. The SAR studies confirm that the addition of a p-nitro phenyl group along with an acidic head may have a significant antidiabetic effect of 134.46 mg/dL which is the same as pioglitazone at 136.56 mg/dL [41].

Azimi, et al. synthesized a few novel pyrazole-benzofuran hybrids and evaluated them for α-glucosidase inhibitory activity. The novel compounds were found to be 4–18 fold more active ($40.6 \pm 0.2 – 164.3 \pm 1.8$ μM) in comparison to the standard drug acarbose with $IC_{50} = 750.0 \pm 10.0$ μM. In this series, compound **(44)** was identified as the most potent derivative with $K_i = 38$ μM. The SAR studies confirmed that the addition of a nitro group on the aryl ring connected to the pyrazole enhances the antidiabetic activity [42].

Sever, et al. designed, synthesized, and biologically evaluated a novel series of pyrazole clubbed with thiosemicarbazones. The synthesized derivatives were biologically investigated for DPP-4 inhibition activity and compound **(45)** with $IC_{50} = 1.266 \pm 0.264$ nM was found to be the most promising compound in this series. This compound was reported to be more active than sitagliptin with $IC_{50} = 4.380 \pm 0.319$ nM. The SAR studies confirmed that the presence of the bromo group in the para position of the benzylidene moiety led to a substantial increase in DPP-4 inhibitory potency. The addition of fluoro and chloro substituents in place of a bromo substituent led to a decrease in DPP-4 inhibitory activity [43].

Datar, et al. reported some novel pyrazole-3-one derivatives. The derivatives were screened for antidiabetic activity. Compound **(46)** with sulphonamide derivative was found to be the most potential compound in this series. The SAR studies indicated that the addition of the 4-acetamido benzene sulphonamide group increases one or two hydrogen bonds. This group might have made the carbonyl group of pyrazole-3-one accessible for binding and thus this compound was found as the most potent and selective PPAR agonist [44].

Naim, et al. designed, and synthesized a novel series of pyrazole coupled with 2, 4-thiazolidinediones as PPAR-ã modulators for diabetes. Fifteen derivatives were synthesized and biologically evaluated. In this whole series, compound **(47)** was reported to be the most potential compound. This compound showed 2.35-fold increase in PPAR-γ gene expression in comparison to rosiglitazone (1.27-fold) and pioglitazone (1.6-fold) as the reference standard drugs. The SAR analysis confirmed that the addition of bulkier hydrophobic groups such as naphthalene moiety increases the antidiabetic activity [45].

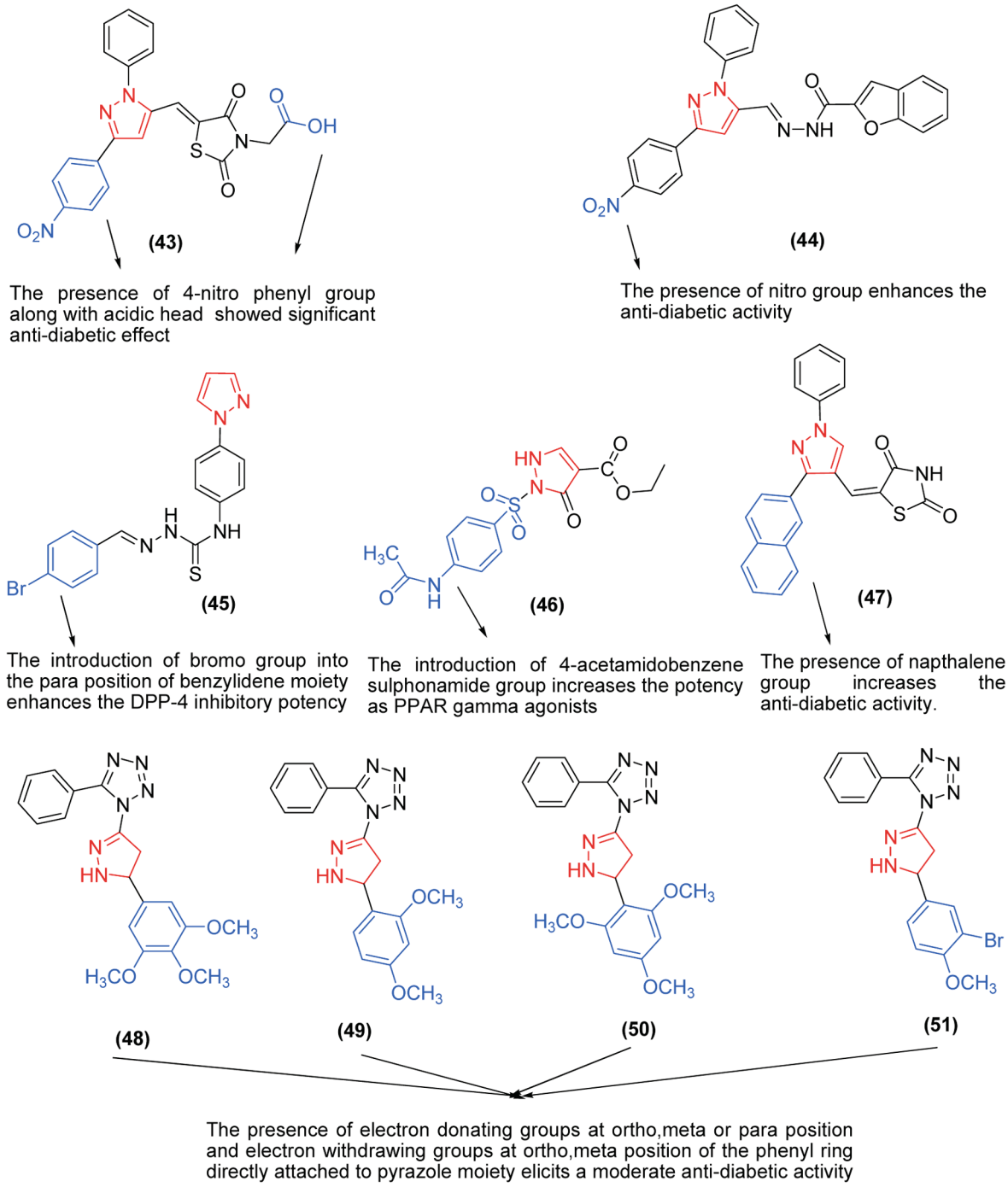


Fig. 5. Chemical structures and SAR studies of potent pyrazole derivatives with antidiabetic activity **(43 – 51)**.

Kaushik, et al. investigated a novel series of pyrazole derivatives. The synthesized compounds were authenticated by spectral data. The derivatives were biologically screened *in vivo* for antidiabetic activity. Derivatives **(48 – 51)** were observed to show prominent antidiabetic activity. The SAR studies confirmed that the presence of electron-donating groups at the *ortho*, *meta*, or *para* position and electron-withdrawing groups at the *ortho meta* position of the phenyl ring directly attached to pyrazole moiety elicits a moderate antidiabetic activity [46].

Pyrazole derivatives with anticonvulsant activity (Fig. 6)

Viveka, et al. designed, synthesized and biologically evaluated a novel series of pyrazole derivatives for anticonvulsant activity. The derivatives were synthesized via the Knoevenagel condensation reaction. The synthesized

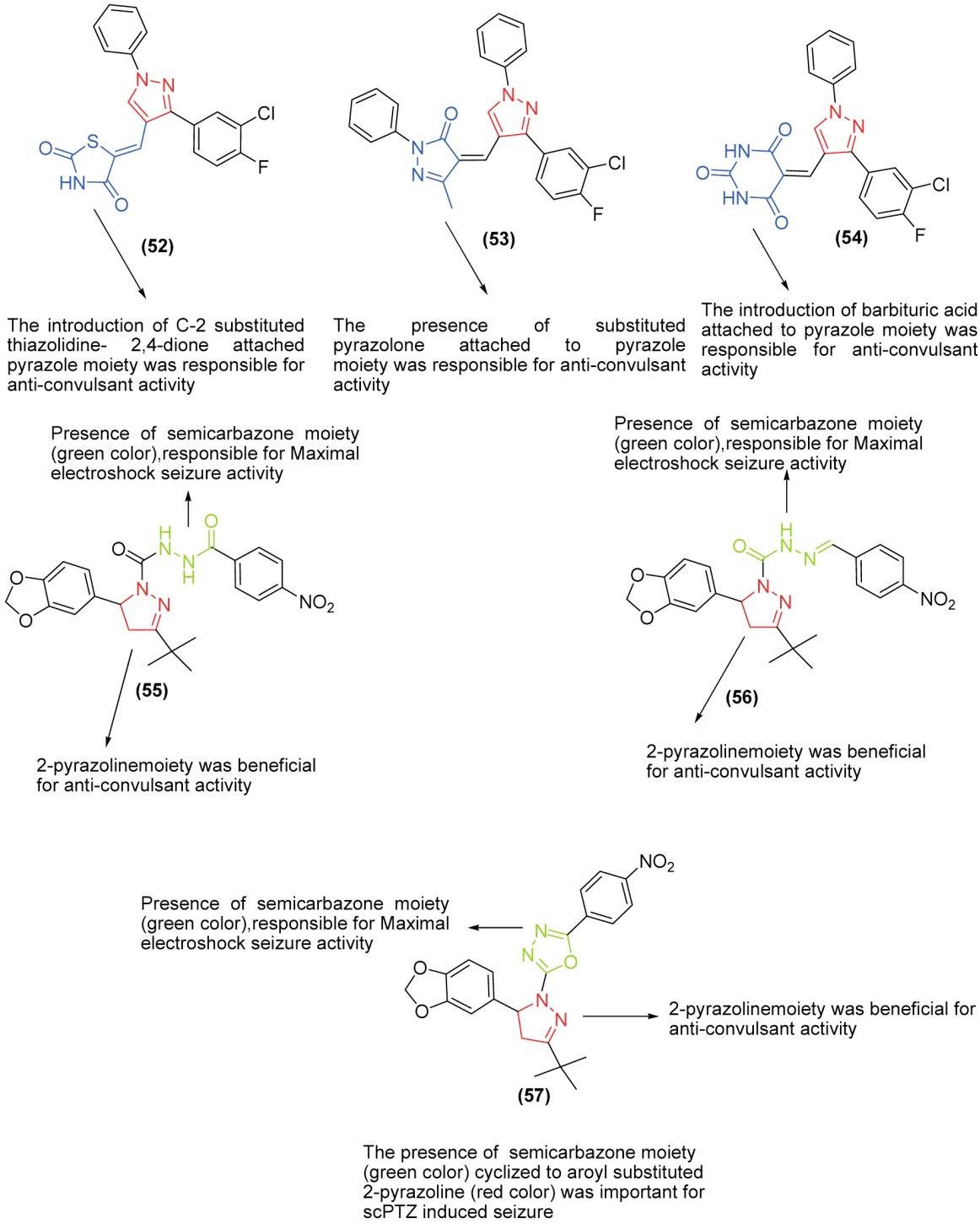


Fig. 6. Chemical structures and SAR studies of potent pyrazole derivatives with anticonvulsant activity **(52 – 57)**.

compounds were characterized by spectroscopic and elemental analysis. Among all the synthesized derivatives, compounds **(52 – 54)** were reported as potent compounds with anticonvulsant activity. The SAR studies of the potent compounds indicated that the introduction of C-2 substituted thiazolidine-2,4-dione substituted pyrazolone and substituted barbituric acid attached to pyrazole moiety emerged as potent derivatives with anticonvulsant activity [47].

El-Behairy, et al. synthesized a few novel pyrazole derivatives using different synthetic methods. The synthesized derivatives were biologically evaluated for anticonvulsant activity. Compounds **(55 – 57)** showed the highest potency.

Compound **(55)** was 2.7 and 1.3 times more active than the stiripentol and lead compound III, Compound **(56)** was 3.3, 1.5, and 1.2 times more potent than stiripentol, lead compound III and compounds **(55)** and **(57)**, being 2.6 times more active than stiripentol. These compounds showed ED_{50} values of 45, 48, and 81 mg/kg, which are higher as compared to stiripentol with ED_{50} = 115 mg/kg and lead compound III with ED_{50} = 110 mg/kg. The SAR analysis confirmed that the presence of a semicarbazone moiety (green color) was beneficial for maximal electroshock seizure activity and the introduction of 2-pyrazoline (red color) was beneficial for anticonvulsant activity [48].

Pyrazole derivatives with antimicrobial activity (Fig. 7)

El-Behairy, et al. reported some novel dihydropyrazole derivatives. The synthesized derivatives were characterized by spectral analysis. The novel candidates were biologically screened for antibacterial activity. The compounds **(58)** with 0.11 μM and **(59)** with 0.12 μM showed the highest activity against *S. aureus*. Furthermore, compound **(60)** was the most active compound with MIC = 0.35 μM for *P. aeruginosa* and *K. pneumonia*. The SAR analysis confirmed that the addition of 2-pyrazoline moiety was responsible for the antibacterial activity and the use of alicyclic amines such as piperidine, and pyrrolidine was beneficial for antibacterial activity [49].

Payne, et al. investigated some novel 3,5-substituted pyrazole analogs. The synthesized derivatives were biologically observed for antibacterial activity. Among different synthesized analogs, compound **(61)** with MIC = 8 μg/mL was found as bacteriostatic. Moreover, this compound was nontoxic for healthy human cells and it interferes with the bacterial morphogenesis in *Bacillus subtilis*. The SAR analysis confirmed that the introduction of 3-methoxy-4-hydroxy (vanillin) moiety was beneficial for antibacterial activity [50].

Zhang, et al. designed, synthesized, and biologically evaluated a novel series of pyrazole carboxamide analogs. A preliminary bioassay study indicated that few targeted derivatives showed good antifungal activities. Among all synthesized analogues, compound **(62)** has the highest antifungal activity (EC_{50} = 0.005 mg/L); moreover, this compound has the highest inhibition ability IC_{50} = 0.034 mg/L). The SAR studies indicated that the addition of diarylamine moiety and pyrazole carboxamide moiety was beneficial for antibacterial activity [51].

Patel, et al. designed and synthesized a novel series of pyrazole coupled with phenothiazines. The synthesized derivatives were investigated biologically for antimicrobial activities. The compound **(63)** was reported as the most active compound with promising antibacterial activity. The SAR studies confirmed that the addition of biphenyl thiazole moiety at the C-5 position of the pyrazole ring and phenyl moiety attached with amide linkage at C-3 of the pyrazole ring was necessary for the antibacterial activity [52].

Pyrazole derivatives with antimycobacterial activity (Fig. 8)

Takate, et al. reported a series of thiazolyl-pyrazole derivatives. All the derivatives were biologically evaluated for antimycobacterial activity. In this whole series, six compounds **(64 – 69)** showed excellent antimycobacterial activity and low cytotoxicity. They concluded that these synthesized compounds could have the potential to treat mycobacterium tuberculosis. The SAR studies concluded that the thiazole ring was responsible for antimycobacterial activity. In addition, the pyrazole ring attached to thiazole ring may have antimycobacterial activity and the addition of a chromone ring was also reported for antimycobacterial activity [53].

Pyrazole derivatives with antineurodegenerative activity (Fig. 9)

Narayanan, et al. designed, synthesized, and biologically investigated the novel series of substituted pyrazoles. The derivatives were evaluated for Alzheimer's disease. In this series, compound **(70)** was considered as a potential compound for Alzheimer's disease. The SAR studies concluded that the addition of 7-substituted coumarin possesses acetylcholinesterase inhibition activity and the substitution of pyrazole on coumarin may show alteration in anti-Alzheimer activity [54].

Li et al. designed some novel derivatives of the fluoro sulphate containing pyrazole ring. The derivatives were biologically evaluated for the treatment of Alzheimer's disease as selective BuChE inhibitors. Among the synthesized analogs, compound **(71)** was observed as potent BuChE (IC_{50} = 0.79 μM) and hBuChE (IC_{50} = 6.59 μM) inhibitors. The SAR studies confirmed that the presence of substituent at the 1-phenyl ring of the pyrazole-5-fluoro sulfate alters the BuChE inhibitory activity. The maximum activity was shown by the chloro substituent. The order of substituent for BuChE activity at the 4-position was: chloro > fluoro > bromo [55].

Liao, et al. designed, synthesized and biologically screened novel and effective pyrazole derivatives. The derivatives were screened as antioxidants for the treatment of neurodegenerative diseases. In this whole series, compounds **(72 – 75)** showed significant protective effects in comparison to edaravone and curcumin, whereas compound **(74)** was reported as the most potent compound for neurodegenerative diseases. The SAR studies concluded that the curcumin moiety possesses a neuroprotective effect. However, the structural instability and low bioavailability may hinder its clinical use. The presence of â-keto structural fragment was related to the low bioavailability. The curcumin-pyrazole derivatives may have antioxidant properties and can antagonize SNP-mediated PC12 cell death. Furthermore, the incorporation of an electron-withdrawing group such as –CN may have neuroprotective effects [56].

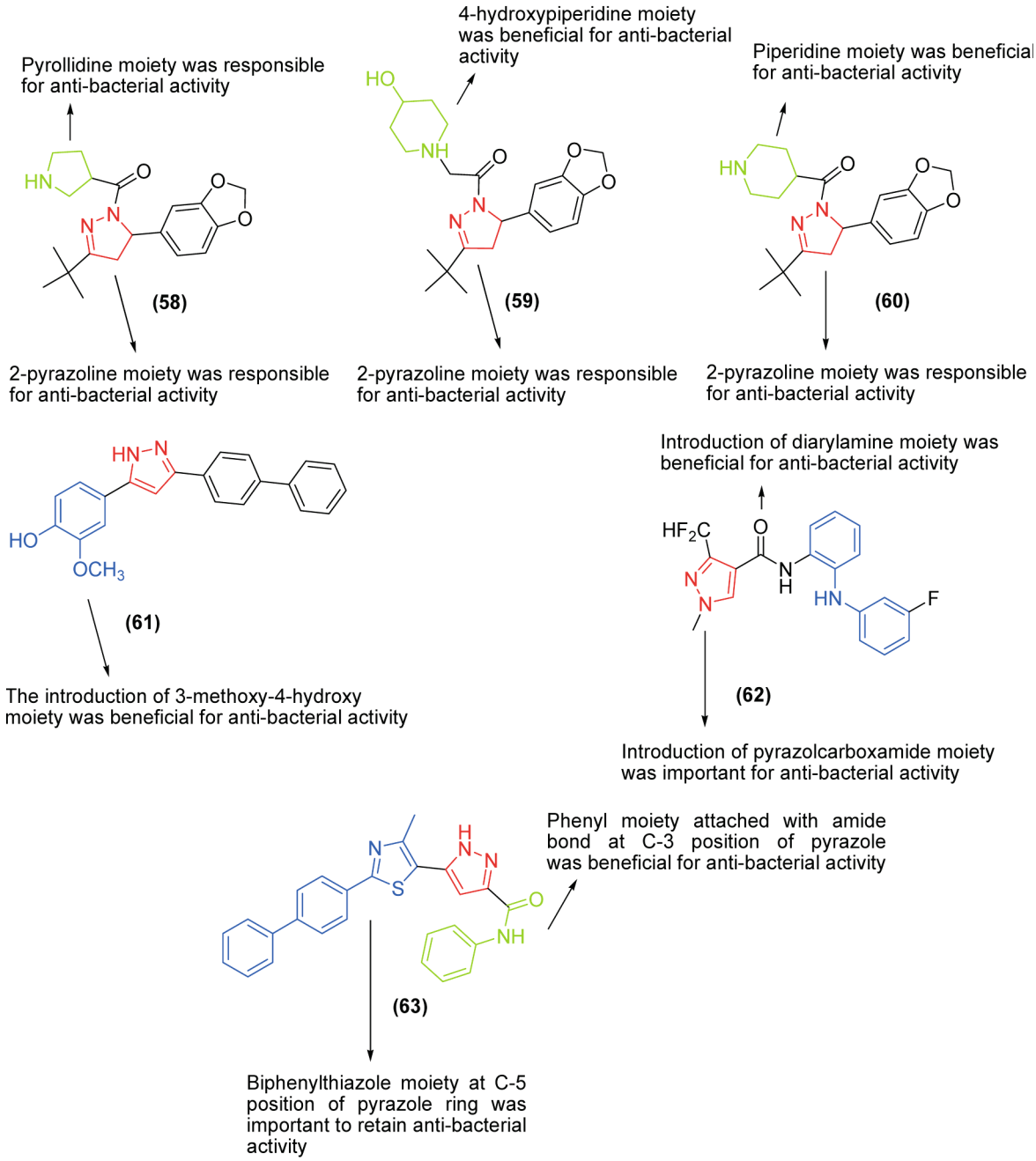


Fig. 7. Chemical structures and SAR studies of potent pyrazole derivatives with antimicrobial activity **(58 – 63)**.

Pyrazole derivatives with antioxidant activity (Fig. 10)

Burgart, et al. designed and synthesized 4-aminopyrazol-5-ols. The novel derivatives were biologically investigated for antioxidant activity. In this series, compound **(76)** was identified as a lead compound. The SAR studies confirmed that the introduction of amino groups and hydroxyl groups in the pyrazole nucleus was important for antioxidant activity [57].

Kumara, et al. identified some novel thienyl-pyrazoles. The compounds were designed, synthesized, and biologically screened for antioxidant activity. The compounds were characterized by using spectral analysis. In this series, compound **(77, 78)** possesses excellent antioxidant activity in comparison to the standard drug ascorbic acid. Compound **(77)** with (IC_{50} = 0.245 ± 0.01 µM) and compound **(78)** with (IC_{50} = 0.284 ± 0.02 µM) may have excellent DPPH activity and are more potent than the ascorbic acid (IC_{50} = 0.483±0.01 µM). These compounds **(77, 78)** also showed hydroxyl radical scavenging activity with (IC_{50} =

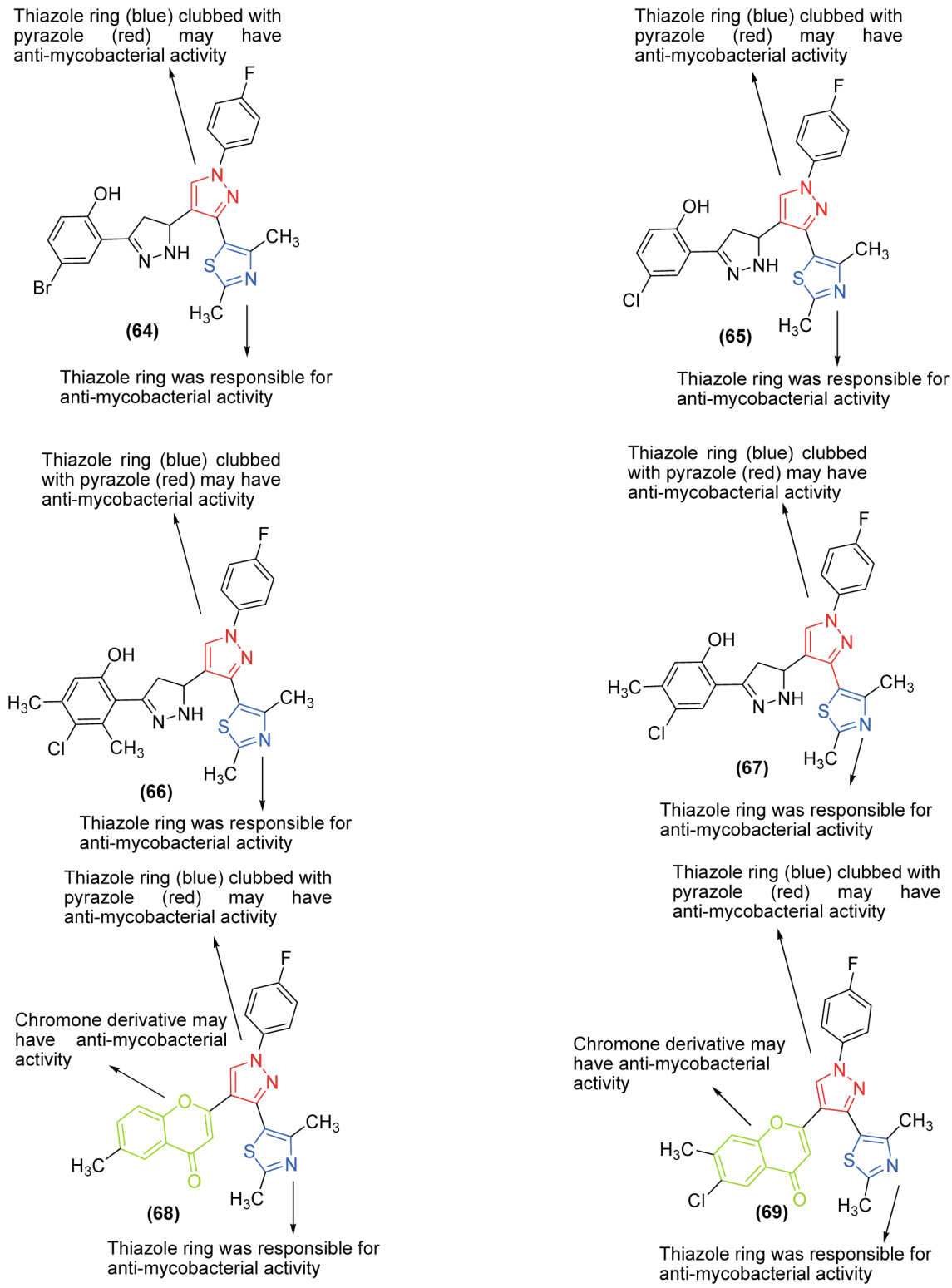


Fig. 8. Chemical structures and SAR studies of potent pyrazole derivatives with antimycobacterial activity **(64 – 69)**.

0.905 ± 0.01 μM), and (IC_{50} = 0.892 ± 0.01 μM), respectively. The SAR studies indicated that the introduction of an electron-donating group such as 4-methoxy, 4-methyl, and 3,4-dimethoxy groups on the C-3 position of the substituted aromatic nucleus may increase the hydroxyl radical scavenging and DPPH activities [58].

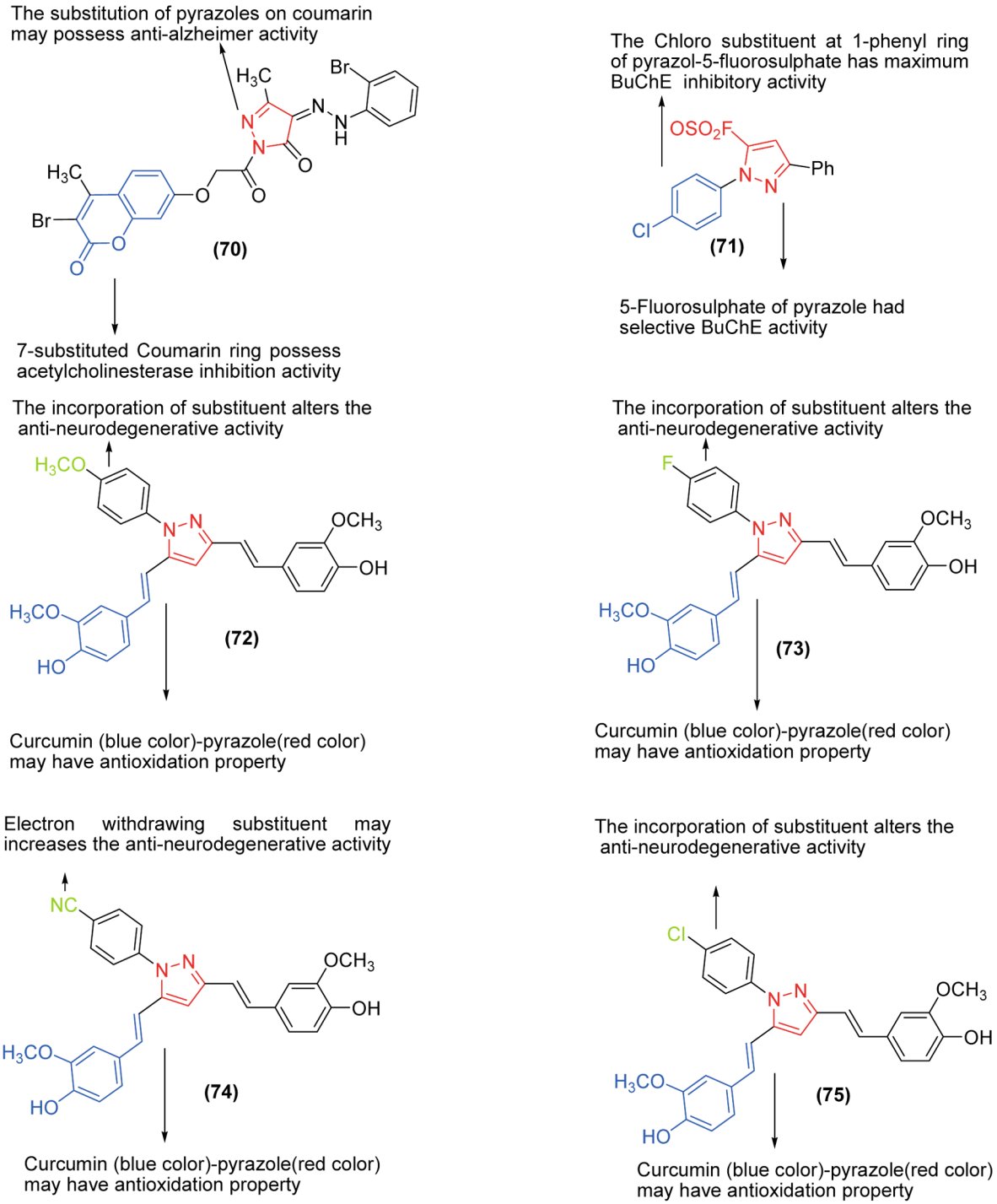


Fig. 9. Chemical structures and SAR studies of potent pyrazole derivatives with anti neurodegenerative activity **(70 – 75)**.

DISCUSSION

Pyrazole is a unique heterocycle consisting of two nitrogen atoms. The versatility of pyrazole moiety shows that it is an essential part of several medicinal agents and some of its derivatives have shown innumerable physiological and pharmacological activities. Due to its remarkable chemical and physical properties, this molecule has gained considerable attention. This moiety can be used as a fundamental framework for numerous pharmacologically active scaffolds. The functionalization of the basic structure of this moiety is a significant goal for the development of potent and novel compounds. Identifying a functional group for a particular activity is a part of the study design and searching for a proper functional group with enhanced activity is the main aim and objective of the research.

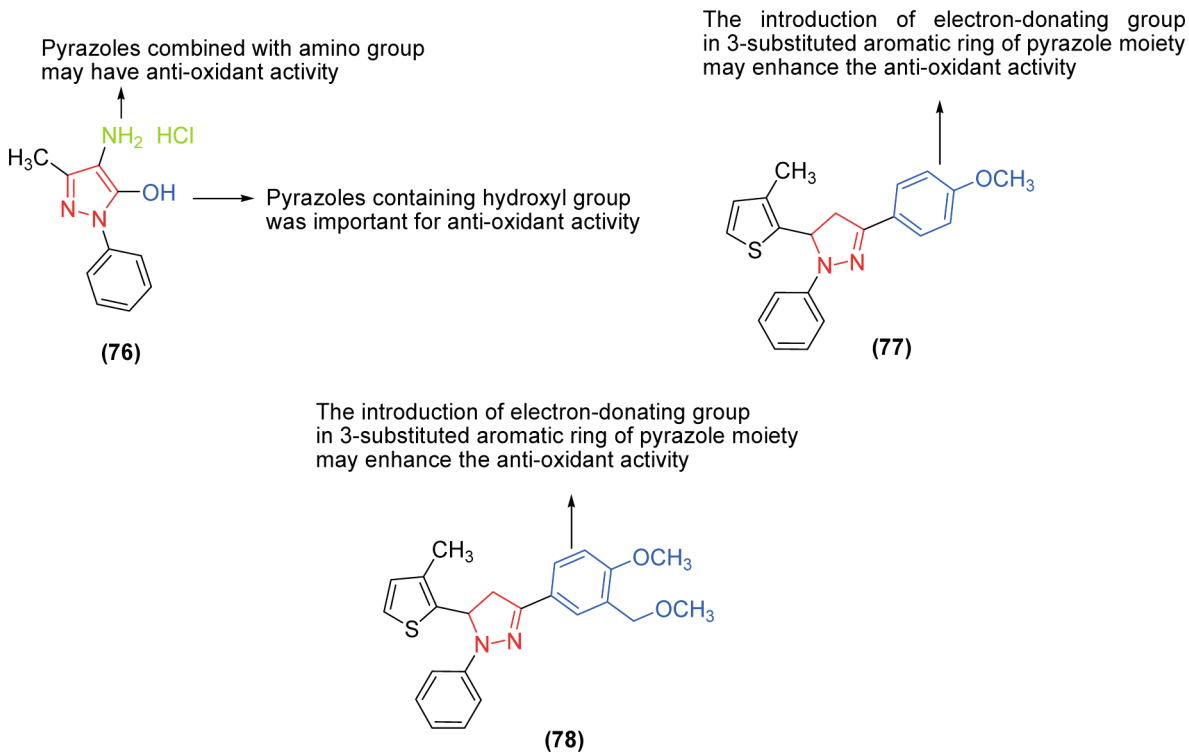


Fig. 10. Chemical structures and SAR studies of potent pyrazole derivatives with antioxidant activity **(76 – 78)**.

CONCLUSIONS

From the literature search, it has been confirmed that the moiety present in the molecules is responsible for their biological activity. Pyrazole is a privileged nitrogen-based heterocyclic compound, that can be present in numerous therapeutically active compounds and have numerous activities. From this review article, it is observed that pyrazole moiety played a beneficial role in the field of medicinal chemistry as it is a structurally simple and bioactive molecule. This molecule can serve as a lead in novel drug design and development with potential biological activity. In the past years, attempts have been made to synthesize biologically active novel pyrazole derivatives and researchers have confirmed that these derivatives have the potential biological activities.

With this review, efforts have been taken to summarize the SAR studies of potent pyrazole derivatives with varying therapeutic activities reported from 2015–2022. Furthermore, patent application published in this period is also discussed. This article will help upcoming researchers interested in synthesizing pyrazole-based molecules.

FUTURE PERSPECTIVE

The study design is a complex process that requires time and energy, but the proper selection of functional groups saves both these parameters. Chemical synthesis is one of the helpful ways to get structural diversification of compounds by adding the needed fragments. Hopefully, this review article can provide a source of information for the organic chemists working on this pharmacophore for the development of novel drugs targeting particular human diseases.

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Authors Contributions

Nitin Gupta contributed to the conception and design of the study, Anandi Kapri contributed to the literature collection and drafting of the manuscript and Sumitra Nain contributed to overall supervision.

Conflict of Interest Statement

The authors declare that there is no conflicttoffinterest.

REFERENCES

1. T. Qadir, A. Amin, P. K. Sharma, et al., *Open Med. Chem. J.*, ***16***, [e187410452202280] (2022).

2. A. Kapri, G. Raj and N. Gupta, *Int. J. Res. Dev. Pharm. Life Sci.*, **7**(2), 2941 – 2948 (2018).
3. M. J. Naim, O. Alam, F. Nawaz, et al., *J. Pharm. Bioallied Sci*., **8**(1), 2 – 17 (2016).
4. A. K. Kabi, S. Sravani, R. Gujjarappa, et al., *Overview on Biological Activities of Pyrazole Derivatives*, In: *Nanostructured Biomaterials. Materials Horizons: From Nature to Nanomaterials*, B. P. Swain (Ed.), Springer, Singapore (2022), pp. 229 – 306.
5. M. Assali, M. Abualhasan, Sawaftah, et al., *J. Chem.,* 1 – 14 (2020).
6. K. Karrouchi, S. Radi, Y. Ramli, et al., *Molecules*, **23**(1), 134 (2018).
7. Z. Cai, W. Zhang, Z. Yan, et al., *Molecules*, **27**, 6274 (2022).
8. M.-C. Ríos and J. Portilla, *Chemistry*, ***4***, 940 – 968 (2022).
9. R. Aggarwal and S. Kumar, *Beilstein J. Org. Chem.*, **14**, 203–242 (2018).
10. A. Ansari, A. Ali, M. Asif, and S. Shamsuzzaman, *New J. Chem.*, **41**(1), 16 – 41 (2017).
11. R. F. Costa, L. C. Turones, K. V. N. Cavalcante, et al., *Front. Pharmacol.*, **12**, 666725 (2021).
12. C. Lianqing, D. Yanting, Z. Quan, and N. Xionglei, China Patent No. 201810399628.1 (2018).
13. S. Dakshinamoorthy, T. Kamaraj, S. Iyengar, et al., U. S. Patent No. US20160244412A1 (2016).
14. M. Sawaguchi and Y. Matsumura, International Patent WO2016158716A1 (2016).
15. L. S. Z. Zhibing, T. Xiaoxuan, W. Lili, et al., International Patent WO2016184310A1, (2016).
16. C. Almansa-Rosales, S. Yenes-Minguez, J. Díaz-Fernández, et al., International Patent WO2018001973A1 (2018).
17. Y. Ishibashi, Y. Ochi, N. Miyake, et al., International Patent WO2016152886A1 (2016).
18. A. Okano and K. Ogawa, U. S. Patent US9777000B2 (2017).
19. G. Meazza, P. Mereghetti, L. Sillani, et al., International Patent WO2015155713A1 (2015).
20. S. Pazenok and N. Lui, U. S. Patent US9914704B2 (2018).
21. Y. Janin, S. Guillou, M. L. Hourani, et al., International Patent WO2015155680A3 (2016).
22. S. Choi, K. Park, H. J. Seo, et al., U. S. Patent US10294207B2 (2019).
23. I. Noriaki, A. Yasuhiro, O. Kazuhiro, et al., International Patent WO2017188357A1 (2017).
24. S. Wassmann, J. Jaunzems, S. Mross, and J. Fabre, International Patent WO2017129759A1 (2017).
25. Q. Yang, B. Lorsbach, D. E. Podhorez, U. S. Patent US9522900B2 (2016).
26. R. K. Plemper, E. Lee, J. Vernachio, and E. Bourque, International Patent WO2017196982A1 (2017).
27. S. Mukherjee, R. Poddutoori and S. Samajdar, Australia Patent 2019247885 (2019).
28. B. Lu, Y. Wang, B. Gui, et al., China Patent 113754685 (2021).
29. X. Tianming, X. Jiahua, Z. Liangkun, et al., U. S. Patent US11104648B2 (2021).
30. D. Hong, Z. Min, W. Zhipeng, et al., China Patent CN111303140A (2020).
31. D. Hong, W. Yang, X. Xiao, et al., China Patent CN111518079A (2020).
32. R. S. Kumar, I. A. Arif, A. Ahamed, and A. Idhayadhulla, *Saudi J. Biol. Sci.*, **23**(5), 614 – 620 (2016).
33. G. S. W. Hassan, D. E. Abdel Rahman, et al., *Eur. J. Med. Chem.*, **171**, 332 – 342 (2019).
34. E. S. Nossier, H. H. Fahmy, N. M. Khalifa, et al., *Molecules*, **22**(4), 512 (2017).
35. A. Masih, A. K. Agnihotri, J. K. Srivastava, et al., *J. Biochem. Mol. Toxicol.*, **35**(3), e22656 (2021).
36. R. Yan, X. Huang, X. Deng, and M. Song, *Polycycl. Arom. Comp*., 1 – 14 (2021).
37. N. M. Saleh, M. G. El-Gazzar, H. M. Aly, and R. A. Othman, *Front. Chem.*, **24**(7), 917, (2020).
38. M. S. A. El-Gaby, M. M. Ghorab, et al., *Med. Chem. Res.*, **27**, 72 – 79 (2018).
39. A. Alsayari, Y. I. Asiri, A. B. Muhsinah, and M. Z. Hassan, *J. Oncol*., 5691982 (2021).
40. R. Alam, D. Wahi, R. Singh, et al., *Bioorg. Chem*., **69**, 77 – 90 (2016).
41. G. Bansal, S. Singh, V. Monga, et al., *Bioorg Chem.*, **92**, 103271 (2019).
42. F. Azimi, H. Azizian, M. Najafi, et al., *Sci Rep.*, **11**(1), 20776 (2021).
43. B. Sever, H. Soybir, Ş. Görgülü, et al., *Molecules*, **25**(21), 5003 (2020).
44. P. A. Datar and S. R. Jadhav, *Int. J. Med. Chem.*, 670181 (2015).
45. M. J. Naim, O. Alam, M. J. Alam, *Arch. Pharm. (Weinheim*), **351**(3 – 4), e1700223 (2018).
46. N. Kaushik, N. Kumar, *Indian J. Pharm. Sci*., **78**(3), 352 – 359 (2016).
47. S. Viveka, D. Dinesha, P. Shama, et al., *RSC Adv.*, **5**(115), 94786 – 94795 (2015).
48. M. F. El-behairy and H. N. H. Attia, *Int. J. Pharm. Pharm. Sci.*, **9**(6), 180 – 188 (2017).
49. M. F. El-Behairy, T. E. Mazeed, A. A. El-Azzouny, et al., *Saudi Pharm. J.*, **23**(2), 202 – 209 (2015).
50. M. Payne, A. L. Bottomley, A. Och, et al., *Bioorg. Med. Chem.*, **48**, 116401 (2021).
51. A. Zhang, J. Zhou, K. Tao, et al., *Bioorg. Med. Chem. Lett.*, **28**(18), 3042 – 3045 (2018).
52. B. Patel, M. Zunk, G. Grant, and S. Rudrawar, *Bioorg. Med. Chem. Lett*., **39**, 127853 (2021).
53. S. J. Takate, A. D. Shinde, B. K. Karale, et al., *Bioorg. Med. Chem. Lett*., **29**(10), 1199 – 1202 (2019).
54. S. E. Narayanan, H. Narayanan, M. Mukundan, et al., *Futur. J. Pharm. Sci*., **7**, 161 (2021).
55. H. H. Li, C. Wu, S. L. Zhang, et al., *J. Enzyme Inhib. Med. Chem*., **37**(1), 2099 – 2111 (2022).
56. L. Liao, J. Shi, C. Jiang, et al., *Neurochem. Int*., **125**, 82 – 90 (2019).
57. Y. V. Burgart, G. F. Makhaeva, O. P. Krasnykh, et al., *Molecules*, **27**(22), 7722 (2022).
58. K. Kumara, M. G. Prabhudeva, C. B. Vagish, et al., *Heliyon*, **7**(7), e07592 (2021).