Pyrazolone structural motif in medicinal chemistry: Retrospect and prospect

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Abstract

The pyrazolone structural motif is a critical element of drugs aimed at different biological end-points. Medicinal chemistry researches have synthesized drug-like pyrazolone candidates with several medicinal features including antimicrobial, antitumor, CNS (central nervous system) effect, anti-inflammatory activities and so on. Meanwhile, SAR (Structure-Activity Relationship) investigations have drawn attentions among medicinal chemists, along with a plenty of analogues have been derived for multiple targets. In this review, we comprehensively summarize the biological activity and SAR for pyrazolone analogues, wishing to give an overall retrospect and prospect on the pyrazolone derivatives.

Keywords

Pyrazolone; Antimicrobial; Antitumor; CNS agents; Anti-inflammatory; Derivatives.

1. Introduction

Pyrazolones delegate a cluster of compounds with the nucleus of 1H-pyrazol-3-ol and pyrazolin-5-one (Fig. 1) which have been investigated because of their multiple features and applications. Since 1883, the synthesis of antipyrine (**1**) by Knorr, numerous attention has caused by the analgesic and antipyretic activities of pyrazolone analogues [1]. The discovery of these features encouraged the researches to synthesize other pyrazolone derivatives with similar behavior but with a better therapeutic action. Nowadays, multiple FDA approved drugs containing pyrazolone nucleus have been explored (Fig. 2), for instances, edaravone (**2**) has been used as free radical scavenger for the treatment of amyotrophic lateral sclerosis (ALS) [2], aminophenazone (**3**) with antipyretic and anti-inflammatory activities has been used in breath tests to measure the cytochrome P-450 metabolic activity in liver function evaluations [3], eltrombopag (**4**) has been used for the treatment of low blood platelet counts in adults with idiopathic chronic immune thrombocytopenia [4], dichloralphenazone (**5**) has been used for the relief of tension and vascular headaches [5], metamizole (**6**) has been used for perioperative pain, cancer pain, acute injury and other forms of pain and is considered as the strongest antipyretic [6]. Several investigational small molecules containing pyrazolone have been regarded as drug candidates including sulfamazone (**7**) [7], propyphenazone (**8**) [8] and nifenazone (**9**) [9].

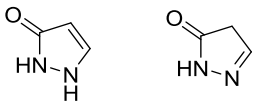


Figure 1. Structure of 1H-pyrazol-3-ol and pyrazolin-5-one.

Regarding pyrazolone derivatives, it is important to underline the enormous diversity of classes of synthetic pyrazolone published in existing studies. As for the pharmacology investigators, this review is a concise and critical account focusing on the properties of pyrazolones as antimicrobial, antitumor, CNS effect, anti-inflammatory, antioxidant, anti-tubercular, antiviral, lipid-lowering, antihyperglycemic agents and protein inhibitors. We summarized advances of pyrazolone derivatives as well as their SAR (**10-189**). Currently, the existing reviews [10, 11] about pyrazolone derivatives are mainly concerning their catalytic asymmetric synthesis or coordination, the comprehensive review of the bioactivity and the SAR studies are still vacant. This review is in order to fill gaps of systematic summarization of biological activities and SAR that could be beneficial for researchers to design novel pyrazolone derivatives, in addition, docking analysis is used to explain interactions between some typical pyrazolone derivatives and potential targets to give a visual appreciation of the roles of pyrazolone group play in the bioactivity.

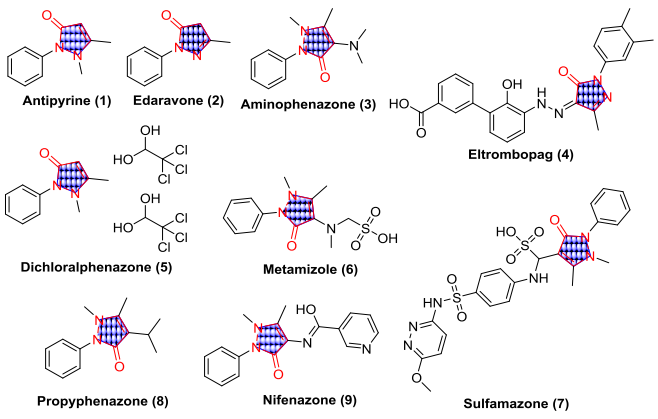
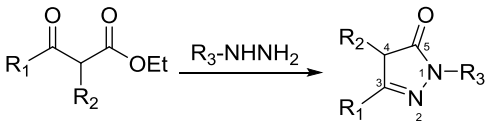


Figure 2. FDA approved drugs containing pyrazolone nucleus and investigational pyrazolone derivatives.

2. Synthetic strategies of pyrazolones

Recent advances in the synthesis of pyrazolones have been reported in the literature [12]. Condensation of hydrazines with β-ketoester compounds is the classical method for the synthesis of pyrazolones (Scheme 1), the catalytic conditions are usually the use of organic base like piperidine or inorganic base like NaH in the system of the boiling ethanol or methanol solvent. The nucleus of pyrazolones has been widely used to ulteriorly synthesize broad range of derivatives including spiroheterocycles and acylation productions [13], which features multiple reactive sites. The electrophilic substitution at the C-4 position of pyrazolones is an effective synthetic route for the construction of pyrazolones linked with chiral groups and 4-disubstituted pyrazolones. In addition, as an important synthon, *α, β*-unsaturated pyrazolones (R_1: C=C-R`/C=N-R`/C=O) can be transformed into diverse pyrazolones. When R_1 is C=C-R`, they can undergo 1,4-Michael addition as acceptors to generate 4-substituted pyrazole analogues.



Scheme 1. Synthesis of pyrazolone nucleus.

3. Pharmacological profile of pyrazolones

The broad-spectrum of pharmacology properties about pyrazolone derivatives have been reported including antimicrobial, antitumor, CNS activity,

anti-inflammatory, antioxidant, anti-tubercular, antiviral, lipid-lowering, antihyperglycemic and protein inhibitory activities.

3.1. Antimicrobial agents

Pyrazolone derivatives have been reported to show the significant antimicrobial activities against multiple types of bacteria and fungi. Generally, the antibacterial effect of pyrazolones is better than its antifungal effect, and the inhibitory activity on Gram positive (Gram $^{+ve}$) and Gram negative (Gram $^{-ve}$) strains was distinct as well.

The bacterial cell membrane is generated with a dense wall comprising several peptidoglycan and teichoic acid layers [14-17]. In Gram $^{+ve}$ bacteria, the adsorption of the biocidal molecules is occurred on the lipoteichonic acid layer which is characterized by the charged nature and the ability to interact with the heteroatoms in the biocide molecules. While in the Gram $^{-ve}$ bacteria, the lipid layer is the target of the biocide molecules. The drug resistance of traditional antibiotics has aroused people`s anxiety about superbacteria, and the attentions giving pyrazolones will pay a light in this field.

3.1.1. Pyrazolones as antimicrobial agents and their SAR

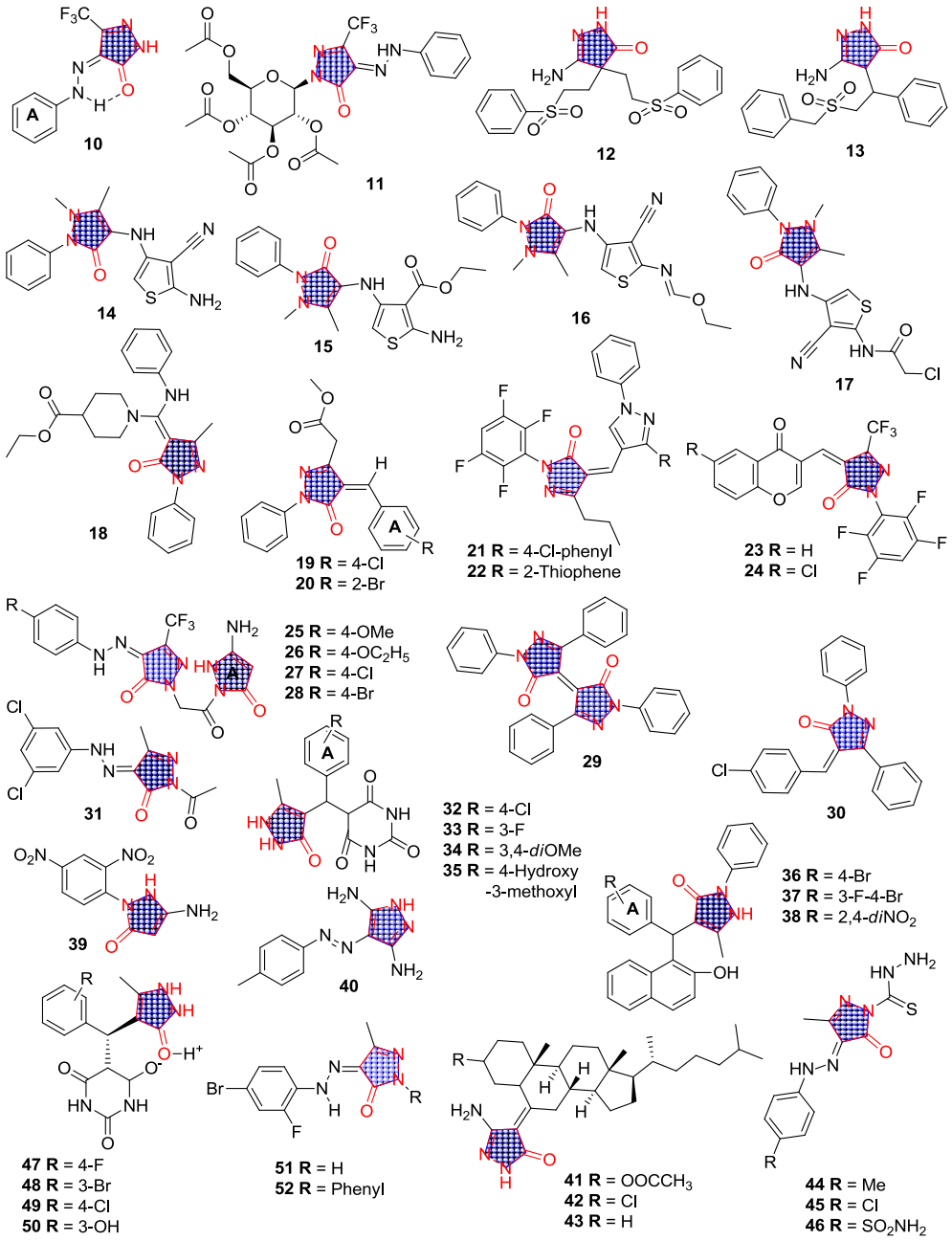


Figure 3. Pyrazolone derivatives with antimicrobial activity.

Nasser S. A. M. Khalil [18] described Schiff base compound **10** and its acetyl glucoside derivative **11** (Fig. 3) which exhibited the most potent inhibitory effect against the strains of *Penicillium italicum*, *Syncephalastrum racemosum*, *Aspergillus fumigatus*, *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli* at the dose of 400 μg/mL. SAR could be deduced that the analogues with non-substituted on ring A exhibited the strongest activity and the acetyl glucoside group was more helpful to

promote the inhibitory effect than *N*-glucoside. It was notable that the possible intramolecular H-bonding formed by the carbonyl group and the NH moiety improved the inhibition and the triad of permeability, solubility, and potency of the analogues were changed accordingly [19].

In 2007, Padmavathi and colleagues [20] synthesized multiple amino-pyrazolone, amino-isoxazolone and amino-pyrimidinone analogues, and evaluated their bioactivities. Thereinto, the amino-pyrazolone derivatives **12** and **13** (Fig. 3) showed the most pronounced antimicrobial activity (Table 1). SAR study elucidated that analogues with amino-hydroxypyrimidinone and *N*, *N*-dimethyliminopyrimidinedione showed weak inhibitory effect when compared with analogues modified with amino-pyrazolone and amino-isoxazolone groups. Additionally, benzyl sulfonyl analogues exhibited strongest inhibitory effect among the productions.

Aly and co-workers [21] synthesized antipyrine derivatives **14**, **15**, **16** and **17** (Fig. 3) which were regarded as the prospective inhibitor (Table 1). SAR investigation expatiated that the presence of pyrazole and the introducing of effective moieties including -$COCH_3$, -CH_3, -Cl and thiophene group on the scaffold of 4-aminoantipyrine showed significant inhibitory effect.

Hamama and teammates [22] described the antibacterial activity of several pyrazolone analogues, among which compound **18** (Fig. 3) was the most hopeful candidate against *E. coli* and *B. subtilis* with the inhibition zoom diameter values of 40 and 36 mm respectively at the concentration of 100 ppm, which was approximately twofold to the reference drug ampicillin. The initiatory SAR can be considered as the

introduction of piperidine group which was helpful to improve the antibacterial effect.

Table 1. Antimicrobial activity as MICS (mg/mL) of pyrazolone derivatives against tested microorganisms.

Com.	MIC (µg/mL)									
	Antibacterial					Antifungal				
	Gram Positive			Gram negative						
	S. aureus	***B. subtilis***	***S. pyogenes***	***P. aerugi nosa***	***E. coli***	***A. fumigatus***	***G. candidum***	***C. albicans***	***S. racemosum***	***A. niger***
12	100	100	-	-	-	-	-	-	-	100
13	25	25	-	-	-	-	-	-	-	50
14	19	9.5	-	39	19	19	19	19	39	-
15	39	19	-	39	19	19	39	78	39	-
16	78	39	-	78	156	78	78	156	625	-
17	39	19	-	39	78	39	78	156	313	-
21	100	100	100	200	62.5	-	-	1000	-	>1000
22	125	125	62.5	250	200	-	-	>1000	-	>1000
23	62.5	62.5	200	500	500	-	-	250	-	>1000
24	250	250	200	62.5	125	-	-	1000	-	500
25	8.02	-	-	9.58	15.28	-	-	9.22	-	5.30
26	12.04	-	-	11.92	26.72	-	-	9.08	-	6.28
27	7.30	-	-	7.39	12.68	-	-	6.18	-	6.80
28	7.96	-	-	10.24	13.27	-	-	8.58	-	7.52
29	-	10.0	-	-	4.08	-	-	-	-	8.16
30	-	-	-	-	-	-	-	-	-	5.1
31	-	≤12.5	≤12.5	≤12.5	>200	-	>200	-	-	-
41	-	-	50	50	50	50	-	25	-	-
42	-	-	50	50	100	50	-	50	-	-
43	-	-	50	50	50	25	-	25	-	-
44	-	-	-	-	125	-	-	7.8	-	2.9
45	-	-	-	-	187.5	-	-	15.6	-	5.8
46	-	-	-	-	125	-	-	11.6	-	5.8
47	-	100	-	-	-	-	-	-	-	-
48	-	25	-	-	-	-	-	-	-	-
49	-	25	-	-	-	-	-	-	-	-
50	100	25	-	-	-	-	-	-	-	-

Note: - not determined.

Active antimicrobial compounds **19** and **20** produced by Rasapalli et al. [23] (Fig. 3) exhibited noticeable antibiofilm activity towards *S. aureus* strains (Table 2). Compound **19** suppressed biofilm formation of *Staphylococcus epidermidis* as well.

SAR study suggested that the antibacterial scaffold can be acquired by condensation of the carbonyl compounds with the active methylene group on pyrazolone, and the 4-Cl and 2-Br substituted groups on A ring were proved to be the potential active modification for further development.

Table 2. Antibacterial effects of compounds **19** and **20**.

Com.	Percent inhibition of overall growth or biofilm formation by 50 μM of compounds							
	Staphylococcus epidermidis GTC 18972		***S. aureus*** ATCC 35556		MSSA		P. aeruginosa MRSA 1094	
	Growth	**Biofilm**	**Growth**	**Biofilm**	**Growth**	**Biofilm**	**Growth**	**Biofilm**
19	32.348	20.421	88.071	88.071	21.951	86.697	38.003	21.468
20	54.976	82.624	-6.961	65.846	8.690	46.471	53.468	87.936

Gadhave and colleagues [24] synthesized multi-fluorinated pyrazole-pyrazolone and chromone-pyrazolone compounds **21, 22, 23** and **24** (Fig. 3) which exerted favorable antibacterial effects (Table 1), whereas all the compounds exhibited poor antifungal activity profile. Regarding SAR, it can be speculated as that multi-fluorinated substitution was contributive to antibacterial while further modification was needed to improve the antifungal effect.

Narayana Rao et al. [25] designed and synthesized several pyrazolone analogues **25, 26, 27** and **28** (Fig. 3) with favorable activity (Table 1). As for SAR, the authors disclosed that the amino group on the A ring of pyrazolone markedly elevated the inhibitory effect compared with methyl, and the antimicrobial sequence of R group on the *p*-position of phenylhydrazine can be generally summarized as: Cl > Br > OMe > OC_2H_5.

In 2017, Abdel Reheim and Baker [26] synthesized multiple pyrazolone derivatives and screened the antimicrobial activity, among which compound **29**

exhibited strongest antibacterial and antifungal activities, and compound **30** (Fig. 3) showed significant antifungal effect (Table 1). The results of antimicrobial test can be concluded as that the introduction of active substitutions such as pyrano, pyridazine and pyrimidine can promote the antimicrobial activity of the pyrazolone nucleus to different degrees.

Alkhaldi et al [27] synthesized pyrazolone derivative **31** (Fig. 3) with multiple antimicrobial effects (Table 1). Concerning SAR, *meta* dichloro phenyl group on the benzene ring of the Schiff base was helpful to improve the antibacterial activity, and the subsequent molecular docking of the interactions of **31** within pontential target glucosamine-6-phosphate synthase (Fig. 4) provided evidence for the antimicrobial effect of **31**, the pyrazolone and the 2,4-dichloro-phenyl moieties made the different binding models between **31** and glucosamine 6-phosphate, but the inhibitory potency is significant as well.

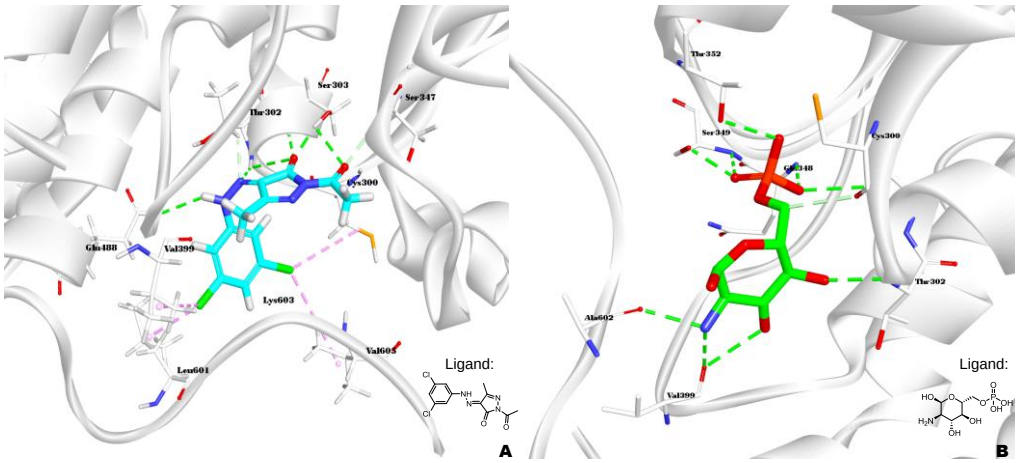


Figure 4. Ligand-protein interactions of compound 31 (**A**) and original ligand (**B**) with the active site of glucosamine-6-phosphate synthase (PDB ID: 2VF5) accomplished by Discovery Studio 2019.

Bhattacharjee and colleagues [28] presented pyrazolone compounds **32**, **33**, **34** and **35** (Fig. 3) which exhibited favorable inhibitory effect against *Bacillus cereus*

with the MIC values of 0.78, 0.78, 0.78 and 0.39 mg/mL, respectively, and suppressed the growth of *Klebsiella pneumoniae* with the MIC values of 0.78, 0.39, 0.39 and 0.78 mg/mL, respectively. The preliminary SAR extracted from the results was that pyrazolone group was necessary to the antibacterial activity and the 3,4-dimethoxyl group on A ring was the potential effective substituent group.

Another research reported that pyrazolone derivatives **36**, **37** and **38** (Fig. 3) were potent compounds with anti-bacterial activity and anti-fungal activity exerted to different degree (Table 3) [29]. In regard to SAR, it was obvious that only compounds **36**, **37** and **38** exhibited anti-fungal activity among the analogues, and in the anti-bacterial evaluation, **36**, **37** and **38** were efficient inhibitor of *S. mutans*, *S. typhi* and *B. subtilis*, respectively. The 4-Br, 3-F-4-Br and 2,4-dinitro groups on the A ring were the potential active groups for further investigation.

Table 3. Antimicrobial zone of pyrazolone derivatives at the dosage of 100 ppm.

Com.	**Antimicrobial zone (mm)**									
	Anti-bacterial activity							**Anti-fungal activity**		
	B. subtilis	***S. mutans***	***M. luteus***	***P. aerugi nosa***	***S. typhi***	***S. paraty phi***	***E. coli***	***C. albica ns***	***T. viride***	***A. niger***
36	18.5	29.5	18.5	14.5	19.5	19.5	-	15.5	13.5	-
37	19.5	18	16.5	14.5	20.5	19.5	-	18.5	10.5	-
38	22.5	14.5	21.5	13.5	20	20	-	28.5	21.5	-
39	18.1	-	-	17.4	-	-	15.3	-	-	15.2
40	25.3	-	-	19.3	-	-	23.1	-	-	25.5

Sayed et al. [30] synthesized active pyrazolone/pyrazole derivatives **39** and **40** (Fig. 3) with antimicrobial activity explored in Table 3. With regard to SAR, compared with the inactive pyrazolone derivative which was non-substituted on the benzene ring, compound **39** exhibited moderate activity in the inhibition zone test.

The pyrazole derivative **40** displayed the strongest inhibitory effect, indicating the potential modification method in the further investigation. The author held the point that the antimicrobial effect of the analogues seemed like their trend in the discrepancy in the polarity and the interaction of analogues by cellular membrane.

Inspired from the structure of cholesterol, compounds **41, 42** and **43** (Fig. 3) were synthesized and investigated for their antimicrobial activities [31]. As shown in Table 1, compounds **41** and **43** exhibited better activity than chloro-derivative **42**, and the stronger antifungal activity were observed than antibacterial activity on steroidal pyrazolones **41, 42** and **43**. Docking study suggested that compound **43** exhibited strongest interactions with S4 active subsite of CYP 51 of *C. albicans* compared with compounds **41** and **42**, in which the oxygen of pyrazolone ring can effectively interact with the H-bond donor and acceptor region.

Ibrahim Ali M. Radini synthesized pyrazolone derivatives **44, 45** and **46** (Fig. 3) as antimicrobial agents (Table 1) [32]. SAR indicated that derivatives with pyrazole-1-carbothiohydrazide moiety exhibited higher inhibitory effect than derivatives containing pyrazolyl thiadiazine moiety. Additionally, the presence of free carbothiohydrazide unit enhanced the activity of compounds **44, 45** and **46** and the presence of electron-donating groups (EDGs) at the aromatic ring promoted the inhibitory effect of compound **44**.

Bihani and co-workers [33] synthesized zwitterionic pyrazolone analogues **47, 48, 49** and **50** (Fig. 3) with the antimicrobial properties listed in Table 1, the moderate inhibitory effects against *Pseudomonas syringae* and *Proteus vulgaris* were also

reported. SAR can be inferred that electrophilic substituted groups on the C-3 or C-4 side of benzene ring could strengthen the activity.

Oraby and teammates [34] synthesized 2,4-disubstituted phenylhydrazonopyrazolone and isoxazolone analogues as antibacterial agents. The results of antibacterial test suggested that the compounds contain the scaffold of pyrazolone like **51** and **52** (Fig. 3) exhibited weak antibacterial effect against the multiple strains. Interestingly, the inhibitory activity was promoted simultaneously when the pyrazolone moiety was replaced to isoxazolone. Furthermore, docking study indicated that cation-π interactions between isoxazolone analogues and Arg 225, which was a residue played a crucial role in the stabilization of the cofactor during the catalysis in flavin adenine dinucleotide, increased the antibacterial effect of isoxazolones. The antibacterial effect of the analogues was influenced by the substitution on C-2 of the phenyl ring, the substitutions with electron withdrawing groups (EWGs) including F and Cl atoms selectivity increased the antibacterial effect against *S. aureus* compared to bulky moieties such like methyl.

3.1.2. Coordination pyrazolone compounds as antimicrobial agents

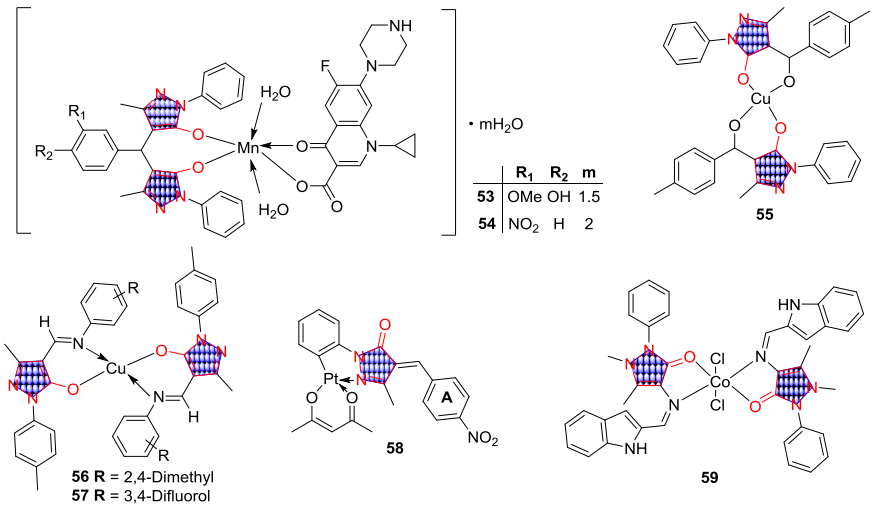


Figure 5. Coordination pyrazolone compounds as antimicrobial agents.

Microorganisms acquire metals from the environment and use them for many essential cellular processes [35]. Metals are able to affect bacterial growth, vitality, and survival [36], and effectively removing metals using metal chelators makes bacterial cells more susceptible to a variety of antibacterial agents, causing cell lysis and loss of viability. Chelators, including EDTA (ethylenediaminetetraacetic acid) and metal complexes of chalcone and flavonoids [37, 38], have attracting attentions in this field. Recently, many research groups made unremitting efforts to the synthesis and characterization of transition metal chelates of pyrazolones. Pyrazolones were likely to form several types of coordination compounds due to the several electron-rich donor centers [39]. Coordination compounds containing pyrazolone-based ligands are reported to be superior reagents in antimicrobial agents. In 2011, a research about Mn(III) mixed-ligand complexes with *bis*-pyrazolones and ciprofloxacin drug was published [40], the antimicrobial outcome showed that when added into the strains of microorganisms (*E. coli*, *Serratia marcescens*, *S. aureus* and *B. subtilis*), the mixed-ligand complexes which contain the moiety of *bis*-pyrazolones and ciprofloxacin exhibited stronger inhibitory effect compared with *bis*-pyrazolones, in which compounds **53** and **54** (Fig. 5) were the potential active antimicrobial agents. SAR can be suspected as that the chelation decreased the polarity of the central atom due to partial sharing of its positive charge with the donor moieties and possible electron delocalization over the whole chelation ring. The complex molecule promoted the hydrophobic character of the metal chelate and the liposolubility, hence favoring its permeation through the lipoid layer of the cell membrane of

microorganism.

Jadeja and co-workers [41] synthesized multiple pyrazolone-based complexes and evaluated the bioactivity. The consequence indicated that compound **55** (Fig. 5) showed stronger inhibitory effect against *B. subtilis* than other derivatives, at the dose of 3 mM, compound **55** suppressed the growth of *B. subtilis* strain with the diameter of inhibition zone of 25 mm.

Schiff bases derivatives of pyrazolone intrigue attention of coordination chemists as versatile spacers due to their viable accessibilities and structural diversity. Joseph et al. [42] prepared two kinds of copper complexes derived from 4-formylpyrazolone (**56** and **57,** Fig. 5) and tested the antimicrobial activity against multiple strains. The result showed that both compounds **56** and **57** suppressed the growth of stains and the effect were quite comparable to the standard drugs including Levofloxacin and Moxifloxacin. 2,4-dimethyl derivative **56** was more effective than 3,4-difluorol derivative **57**.

Lunagariya et al. [43] synthesized several organometallic platinum (II) analogues containing pyrazolone and determined their bioactivities. Among the analogues, compound **58** (Fig. 5) displayed the strongest antimicrobial activities against *P. aeruginosa, B. subtilis, S. Aureus, S. marcescens* and *E. coli* with the MIC values of 35 μM, 30 μM, 25 μM, 22 μM, and 32 μM, respectively. SAR research can be recapitulated that inhibitory effect was influenced by introducing different substitutions on A ring. The presence of methoxyl group at 4-position on of A ring exhibited significant antibacterial activity against Gram $^{+ve}$ bacteria i.e. *B. substiles*

and *S. aureus*. Moreover, the nitro and bromo groups at 4-position on A ring increased antibacterial activity against *B. substiles* and *S. marcescens*. The presence of EWGs on A ring of complexes exhibited better antibacterial activity against Gram $^{+ve}$ and Gram $^{-ve}$ micro-organism than other EDGs in complexes.

Nair and co-workers [44] prepared some metal complexes with derived from pyrazolone and evaluated their antimicrobial potent. The synthetic analogues exhibited antimicrobial effects to different degrees, among which compound **59** (Fig. 5) was the most promising one with the highest zones of inhibition i.e. 10.5, 14.3 and 11.2 mm measured in *P. aeruginosa, S. aureus* and *E. coli*. SAR research suggested that the metal chelates were more toxic than the parent ligands against the same microorganism and under identical experimental conditions. The biological activity of complexes followed the order of the change of metal ion: Ni (II) > Co (II) > Zn (II) > Cu (II) > Schiff base ligand.

3.2. Antitumor agents

In the 21st century, malignant tumor is one of the leading causes of death and developing new antitumor agents with less drug resistance and side effects needs to be done as soon as possible [45]. In recent years, pyrazolone derivatives and their metal complexes have attracted the great attention of researchers for their potential antitumor activity and their less drug resistance and side effects [46]. So far, diverse pyrazolone analogues with antitumor potency have been reported.

3.2.1. Pyrazolones as antitumor agents and their SAR

3.2.1.1. VEGFR-2 target inhibitors

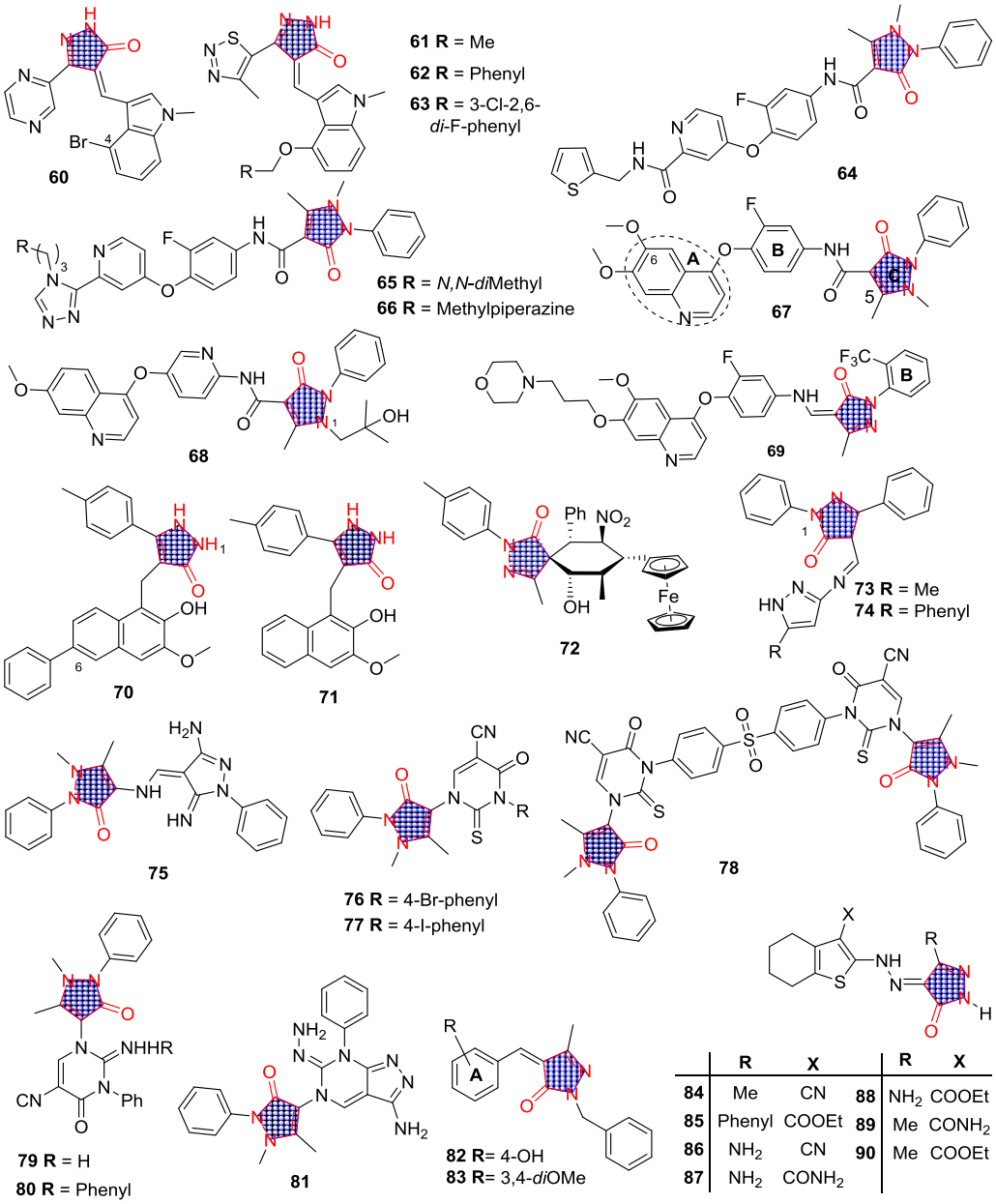


Figure 6. Pyrazolone derivatives with antitumor activity.

Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2), also known as Flk-1, is mainly expressed in vascular endothelial cells and hematopoietic stem cells [47]. It is highly expressed in a variety of malignant tumors and plays a significant regulatory role in the metastasis and angiogenesis of tumor. Taking VEGFR-2 as the target, the search for VEGFR-2 inhibitors provides a good way to find some new anticancer drugs. Based on conserved active binding sites of VEGFR-2 and similar interaction conformation with ligands, several novel inhibitors of VEGFR-2 have

been developed [48], in which pyrazolones play important roles as well.

In 2006, Tripathy and co-workers [49] synthesized a train of heterocyclic-substituted pyrazolones and tested inhibitory potency against VEGFR-2 kinase, among which compound **60** (Fig. 6) was proved to be the most potential derivative inhibiting VEGFR2 kinase with the IC_{50} value of 6 nM. SAR for the analogs can be summarized that replacement on the indole ring exhibited further potency increase against VEGFR-2 especially at the position of C-4 on the ring.

Inspired from existing VEGFR-2 inhibitors, the same research group [50] modified the structure **61** by introducing a 4-benzyloxy substituent to generate compound **62**. Further investigation on structural modifications of the aromatic moiety of **62** revealed that compound **63** (Fig. 6) was the most promising anaplastic lymphoma kinase (ALK) inhibitor (IC_{50}: 5 nM). As for SAR, it was demonstrated that a plenty of halogen substituent groups on the aromatic ring were favored for ALK inhibitory potency. Moreover, the authors paid attention to the modification of the heterocyclic moiety and SAR analysis was concluded that compound bearing thiazole increased inhibition of ALK.

Gu et al. [51] prepared a series of novel pyridine analogues bearing pyrazolone skeleton and evaluated the cell proliferation activities of synthetic analogues. Among all compounds, **64**, **65** and **66** (Fig. 6) exhibited favorable inhibitory potential on c-Met and VEGFR-2. The most promising analogue **66** significantly inhibited the targets c-Met (IC_{50}: 0.11 μM) and VEGFR-2 (IC_{50}: 0.19 μM) kinases *in vitro*. SAR analyses suggested that substitution of pyridine amine moiety with longer polar side chains or with hydrophilic group could improve inhibitory activity.

3.2.1.2. c-Met target inhibitors

Receptor tyrosine kinase c-mesenchymal epithelial transition factor (c-Met), a vital target in antitumor therapy, plays a crucial role in the occurrence, development, metastasis and angiogenesis of tumors. In 2012, according to the theory of Structure-Based Drug Design, Norman and co-workers [52] designed and synthesized a series of class II c-Met inhibitors, among which derivative **67** (Fig. 6) was confirmed to possess excellent potency against c-Met (Ki: 1.0 nM). This privilege compound was demonstrated to show binding affinity not only with c-Met (PDB ID: 3U6H) (Fig. 7A), but also with VEGFR-2 kinase (PDB ID: 3U6J) (Fig. 7B) with the help of X-ray analysis of cocrystals. Obviously, the pyrazolone moiety plays crucial roles in occupying active sites of binding pocket, forming the pi-alkyl with Val 1155 in c-Met and H-bond with Asp 1046 in VEGFR-2 kinase, suggesting the broad prospect of pyrazolones developing as antitumor agents in the future. This study provides a new strategy for designing more selective analogues. Therefore, Liu et al. [53] synthesized a cluster of pyrazolone-based analogues according to compound **67** and screened the most selective class II c-Met inhibitor. Among them, compound **68** (Fig. 6) was the representative active antitumor agent. SAR investigation revealed that the 6-methoxy group of quinoline in the region (A), the pyridine in the central ring (B) and 2-hydroxypropyl side chain at N-1 could promote the selectivity and activity. In addition, the polar functionality at C-5 position of the pyrazolone was important for selectivity.

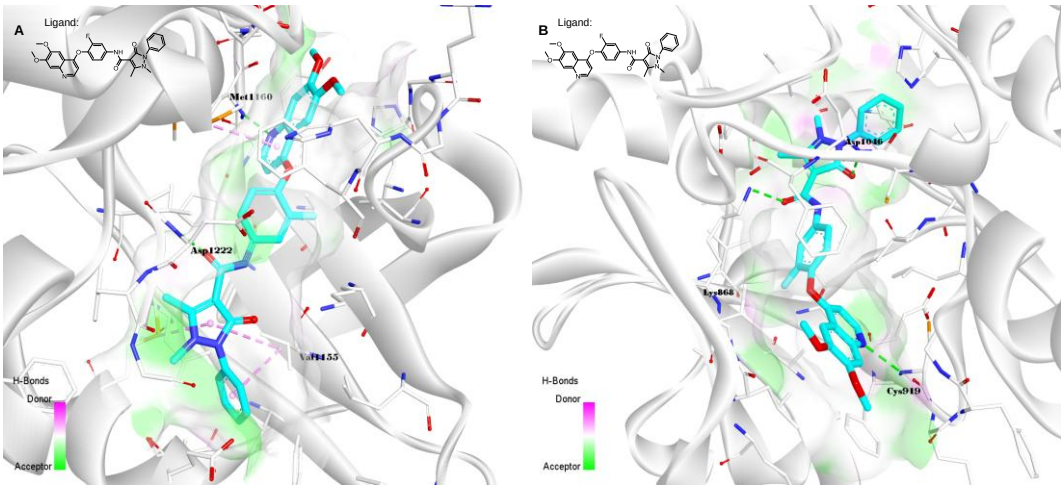


Figure 7. Resolved pharmaceutical cocrystal of pyrazolone derivative **67** with c-Met (**A**, PDB ID: 3U6H) and VEGFR-2 kinase (**B**, PDB ID: 3U6J).

A potential compound **69** (Fig. 6) was designed and synthesized by Zhou and colleagues [54], inspired from the structure of abozantinib and foretinib as c-Met inhibitor (IC_{50}: 2.20 nM) to show antiproliferative effect against multiple cancer cell lines, respectively. SAR investigation could be concluded that substitution of the cyclopropane-1,1-dicarboxamide framework of foretinib with the *N*-aryl-pyrazolone-4-imino and 2,4-imidazolinedione group sustained the potent antitumor activity. Additionally, analogues with mono/double-EDGs on the ring B were more active, especially -CF_3 at the C-2 position of ring B were more effective than -CH_3 or -OCH_3 groups.

3.2.1.3. Other antitumor pyrazolone derivatives

Human SIRTs (Sirtuins) are relative to cell senescence, apoptosis, metabolism, proliferation and differentiation. In the past decade, they have emerged as targets for cancer chemotherapy. SIRT1, SIRT2 and SIRT3 are relatively important in the SIRTs family with extensive research. Mahajan and teammates [55] prepared a multiple of five-membered ring pyrazolone analogues as Sirtuin inhibitors. Among these products, compounds **70** and **71** (Fig. 6) showed the inhibitory activities against SIRT1 with

IC_{50} values of 41 μM and 27 μM, respectively. In addition, compound **70** displayed the most promising inhibitory effect against SIRT3 (IC_{50}: 6 μM). According to the pharmacophore investigations, SAR can be sum up as the presence of pyrazolone ring was important to improve the inhibitory effect on SIRT1 and SIRT3 through maintaining the balance of H-bond donor and acceptor moieties, from the active analogue **71**, the introduction of bulky hydrophobic benzene group at the C-6 position of naphthalene was helpful to increase the activity on SIRT3. Moreover, the selective inhibition on SIRT2 was significantly elevated when the H-bond donor NH group on the position 1 was replaced as H-bond acceptor O.

It's reported that pyrazolone was potential to be the starting point for generating RalA inhibitors, which were often activated in human cancer cell lines. Derivative **72** (Fig. 6), as the most promising anticancer candidate, was designed and synthesized by Zhang and colleagues. [56] The consequence for ability of compound **72** inducing apoptotic death in PANC-1 cells showed that derivative **72** suppressed RalA according to inducing the accumulation of ROS and trigger mitochondrial apoptosis in PANC-1 cells.

Markovic and colleagues [57] designed and synthesized compound **73** and its 5-phenylpyrazole derivative **74** (Fig. 6) which exhibited the most promising activity (Table 4). QSAR study revealed that geometrical and topological are the most momentous factors for effect of the analogues, for instance, the size and shape of the molecule. Containing planar benzene group at N-1 position of pyrazolone showed superior inhibitory potency on both cells tested for it was a more favorable conformation moiety when interacting with active sites. Herein, the inhibitory effect

on the target mostly depended on fragment at the C-4 position through forming H-bonds with active place.

Table 4. Cytotoxic activity as IC_{50} (µM) of pyrazolone derivatives against tested cell lines.

Com.	*In vitro* cytotoxicity IC_{50} (µM)		
	MCF-7	MDA-MB-361	MDA-MB-453
73	—	9.98	10.24
74	—	12.17	8.75
75	60.72	—	—
76	43.41	—	—
77	30.68	—	—
78	37.22	—	—
79	54.23	—	—
80	44.99	—	—
81	44.99	—	—

Pyrazolone derivatives such as 4-aminoantipyrine are well known compound used widely prophylactic of some diseases including cancer. Ghorab and colleagues [58] synthesized a variety of pyrazolone derivatives **75-81** (Fig. 6) inspired from 4-aminoantipyrine and determined the anticancer activity (Table 4). SAR study can be summarized that the most potent compound belonged to the pyrimidine derivatives especially the halogen group.

Dube and colleagues [59] synthesized a cluster of pyrazolone heterocyclic derivatives and evaluated their cytotoxic activities *in vitro*. The results of brine shrimp lethality assay showed that compound **82** displayed a favorable cytotoxic activity than standard cyclophosphamide. In addition, compounds **82** and **83** (Fig. 6) were found to be prominent analogues with the lethality concentration (LC_{50}) values being 10.8 µg/mL and 14.5 µg/mL in sulforhodamine B (SRB) assay, respectively. SAR investigation implied that the dimethoxy substitution on ring A increased the antitumor activities, the group of hydrophobicity and hydrophilicity played a significant role in cytotoxic activities.

Gouda et al. [60] prepared several pyrazole analogues and tested the cytotoxicity against the *Ehrlich ascites* carcinoma cells (EAC). To detail, the cytotoxicity data clearly displayed that and compounds **84** and **85** exhibited favorable activities compared with 5-fluorouracil (Table 5). SAR can be recapitulated that introducing a hydrazopyrazol-5-one ring in position 2 to benzothiophene was important to the cytotoxic activity, furthermore, the order of antitumor activities of compound follows **86** < **87** < **88** and **84** < **89** < **90** (Fig. 6), it can be speculated that the group of COOEt at position 3 of the thiophene ring system in compounds increased the antitumor activity.

Table 5. *In vitro* cytotoxicity of tested compounds (*Ehrlich ascites* cells apoptosis %).

Com.	% Apoptosis		
	100 µg/mL	**500 µg/mL**	**25 µg/mL**
5-Fluorouracil	97.3%	68%	38.6%
84	84%	53.3%	29.8%
86	100%	98.6%	94%
87	98.4%	81%	65%
88	98.1%	79%	60%
89	96.5%	66.6%	38.1%
90	79.4%	71%	43%

3.2.2. Coordination pyrazolone compounds as antitumor agents

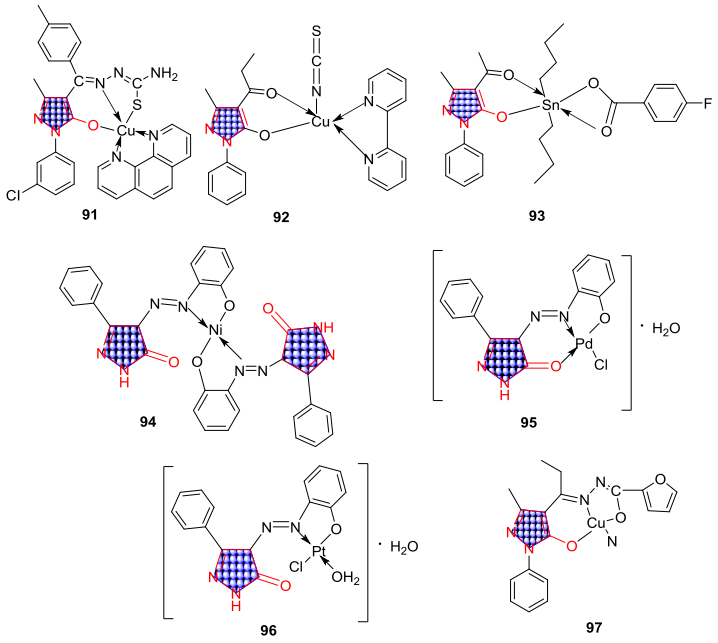


Figure 8. Coordination pyrazolone compounds as antitumor agents.

In 2013, Vyas and colleagues [61] synthesized the new pyrazolone based complex **91** (Fig. 8) for the first time, which was suggested to be a potent antitumor agent against lung cancer cell lines (A549). According to evaluation of the cytotoxic activities against A549 cell lines and noncancerous rat cardiomyocytes (H9C2) cell lines *in vitro*, the result displayed that compound **92** (Fig. 8) possessed a superior cytotoxic property. Moreover, LDH activity of compound **92** showed the higher levels in the culture medium treated with A549 cells. It was worth mentioning that the chelation of Cu (II) with the pyrazolone and bipyridyl ligands formed the π-π* conjugation in which gave the extended planar structure resulting in the superior cytotoxic property.

Zhao and colleagues [62] prepared a cluster of novel mixed-ligand dibutyltin (IV) complex pyrazolone, all of the synthesized complexes were screened against two human cancer cell lines (KB and HeLa) *in vitro* and utilized MTT assay to evaluate antitumor activity. The results suggested that all complexes display a favorable antiproliferative activity against KB and HeLa cell lines with the IC_{50} values ranging from 0.29 to 0.54 μM for KB and 0.05-0.31 μM for HeLa. Compound **93** (Fig. 8) exhibited the most potent activity (IC_{50}: 0.05 μM) against HeLa cell. SAR study implied that acetyl from acylpyrazolone and *para*-fluorobenzoate ligand may play a considerable role for increasing the antitumor activities.

Three kinds of pyrazolone complexes **94-96** (Fig. 8) were synthesized by Bakr and co-workers [63]. The MTT assay outcomes implied that HL exhibited the better cytotoxic activity against HePG2 and PC3 cell lines than 5-Fluorouracil with IC_{50}

values being 5.69 and 6.80 µg/mL, respectively (Table 6). For metal complexes, the order of cytotoxicity was found to be **95** > **94** > **96**.

Table 6. *In vitro* cytotoxic activity of compounds **94-96** towards the cell lines.

Com.	In vitro cytotoxicity IC_{50} (µg/mL)			
	HePG2	**HCT-116**	**PC3**	**MCF-7**
5-Fu	7.9	5.2	8.3	5.5
94	15.31	16.93	17.30	27.47
95	10.73	14.65	11.45	12.96
96	28.30	20.59	20.40	35.62

Zhang and colleagues [64] synthesized two new transition metal complexes with 4-acylpyrazolone derivative as potential antitumor agents. According to the results of antitumor determination, the complex **97** (Fig. 8) was proved to exhibit higher cytotoxicity activity with IC_{50} values being 1.9 µg/mL for human esophageal cancer cells (Eca- 109) and 1.2 µg/mL for cervical cancer cells (HeLa). The study suggested that the complex **97** might be an effective agent for tumor.

3.3. CNS agents

Because of the intricate pathogenesis and devastating effects, CNS disease is still a challenge for researchers to find novel precursors as the therapy [65]. In view of the experiment of the development of edaravone, several pyrazolones have been taken into account to be the CNS agents, existing literatures mainly focus on the anticonvulsant, antidepressant, anti-amyotrophic lateral sclerosis, anti-Alzheimer's activities and inhibitory effect against other CNS related targets. Herein, we summarized the bioactivity and SAR for the synthetic derivatives, wishing to give evidence for pyrazolones to develop as CNS clinical agents.

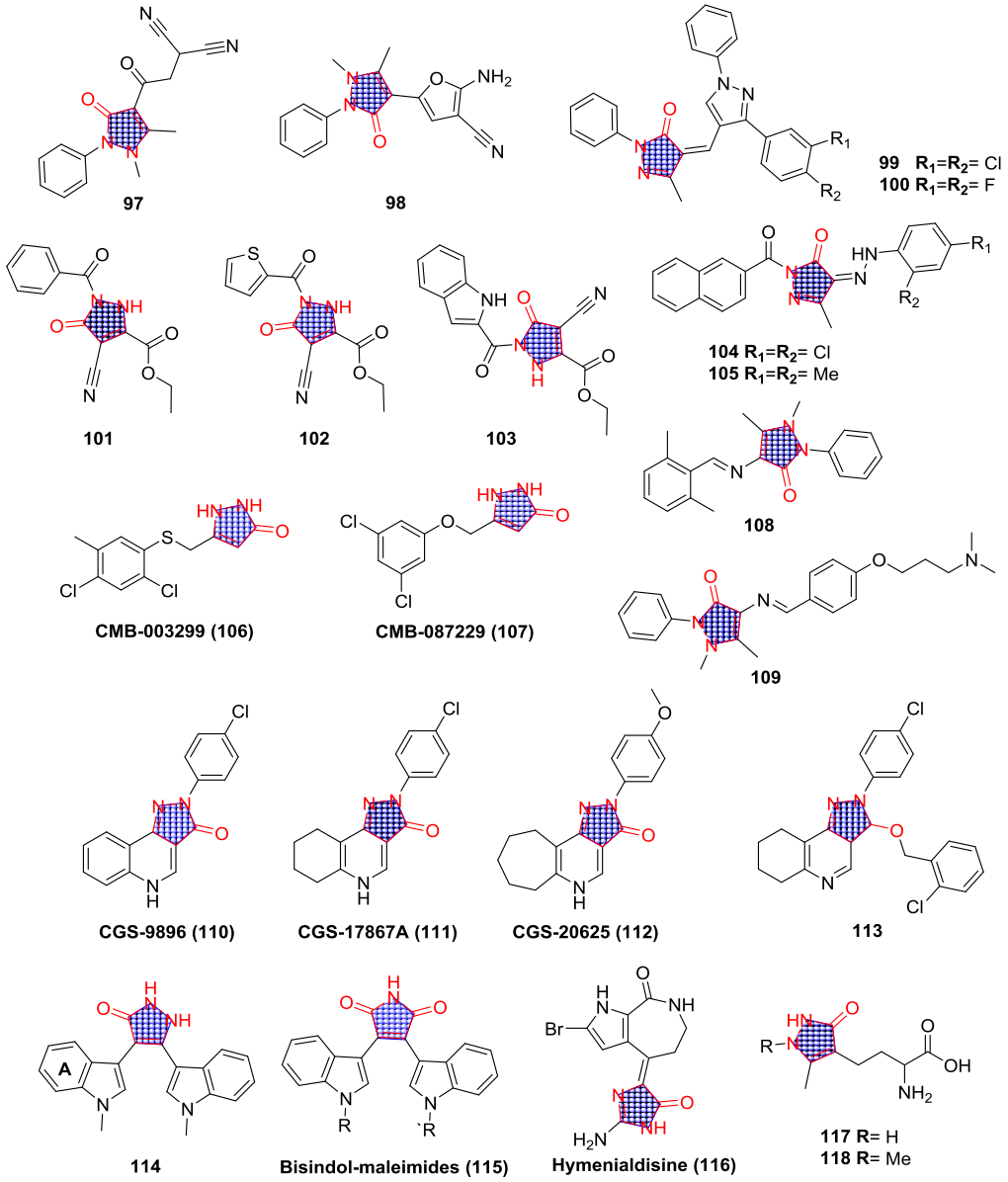


Figure 9. Pyrazolones as CNS agents.

3.3.1. Anticonvulsant agents

Epilepsy is a chronic neurological disorder syndrome identified by the spontaneous recurrence of seizures which can disrupt periods of more or less normal electroencephalographic (EEG) activity and behavior [66]. Currently the anticonvulsant drugs are chiefly derived from benzodiazepines or GABA (γ-aminobutyric acid) analogues, pyrazolone derivatives are likely to provide a novel orientation for drug design. Eldebss et al. [67] synthesized pyrazolone-based

heterocycle compounds as monoamine oxidase (MAO) inhibitors and evaluated the tryptamine seizure potentiation in rats. The results manifested that compounds **97** and **98** (Fig. 9) were the most promising candidates (Table 7).

Table 7. Bioactivity of compounds **97** and **98**.

Com.	K_i (nM) MAO-A	K_i (nM) MAO-B	SI[a]	MAO-A IC_{50} (nM)	MAO-B IC_{50} (nM)	ED_{50} (μM) *in vivo*
Deprenyl	-	-	-	3.90×10^{-6}	3.00×10^{-8}	0.30
97	0.014	121.34	8667.143	2.34×10^{-6}	13.23×10^{-8}	19.23
98	0.346	765.87	2213.497	7.99×10^{-6}	45.43×10^{-8}	47.54

[a]SI (selectivity index) = Ki (MAO-B)/Ki (MAO-A) ratio

Viveka et al. [68] prepared pyrazolone analogues **99** and **100** (Fig. 9) with favorable anticonvulsant activities. In the maximal electroshock (MES) test, compound **99** performed the best protective potency with the protection ratio of 79.76% and no significant toxicity was determined at the dosage of 25 mg/kg, while in the analgesic test it showed weak effect. Compound **100** exhibited moderate protection on the reaction time of mice. SAR study demonstrated that the existing of pyrazolone moiety elevates the anticonvulsant potency. As for the analgesic effect *di*-Cl substituent group on the heterocyclic systems promoted the activity, whereas slightly less activity was determined for the analogues with *di*-F substituents.

A cluster of pyrazolone analogues were synthesized and assessed for the anticonvulsant and antidepressant activities by Abdel-Aziz and colleagues [69]. Compounds **101, 102** and **103** (Fig. 9) displayed the most potent protective potency against pentylenetetrazole (PTZ)-induced clonic seizures in mice at a dosage level of 20 mg/kg with the protective ratio for 74.5, 78.7 and 74%, respectively, which was close to phenobarbital sodium (30 mg/kg) and better than phenytoin sodium (30

mg/kg). Preliminary SAR study can be concluded that the existence of cricoid pyrazolone group increased the anticonvulsant effect compared with the linear chain-hydrazide analogues, and thiophene acyl moiety was the most potent substituted group, while linear chain-hydrazide analogues performed better than pyrazolones in the antidepressant determination.

3.3.2. Antidepressant agents

Merugumolu and co-workers [70] prepared multiple pyrazolone derivatives and estimated the anti-depressant effect *in vivo*. The consequence demonstrated that the most promising derivatives **104** and **105** (Fig. 9) possessed remarkable anti-depressant activity in forced swimming test and tail suspension test (Table 8), with the relative values in the same magnitude of imipramine. As for SAR, the substituted groups on the 3,4-position of the ring of aromatic hydrazine exhibited better activity than other substituted groups.

Table 8. Antidepressant effect of compounds **104** and **105**.

Com.	**Forced swimming test**		**Tail suspension test**	
	Duration of immobility (s)	**Change in immobility (%)**	**Duration of immobility (s)**	**Change in immobility (%)**
Control	203.3	---	185.8	---
Imipramine	94.0	-53.8	109.0	-41.3
104	97.7	-51.9	114.3	-38.4
105	129.5	-36.3	111.0	-40.2

3.3.3. Anti-amyotrophic lateral sclerosis agents

The pyrazolone skeleton is an effective group characterized in a cell-based high throughput screening assay targeting mutant Cu/Zn superoxide dismutase 1 (SOD1) induced toxicity and aggregation as a marker for amyotrophic lateral sclerosis (ALS), which is an orphan neurodegenerative disease so for without a cure with the incidence

of 1-2 per 100000 per year and 2-5 years from diagnosis to death [71, 72].

A cluster of pyrazolone analogues were screened and evaluated for the anti-ALS activity from FDA approved drugs and biochemical reagents by Radhia and co-workers [73], as the most potent skeleton, the arylsulfanyl pyrazolones showed 100% efficacy compared with the positive control, radicicol (80% efficacy) in the test of G93A-SOD1 expression in PC12 cells model. CMB-003299 (**106**, Fig. 9) was the typical compound to decrease the mutant SOD1 aggregation with the ED_{50} value of 400 nM, and the weak cytotoxic effect was detected with the LD_{50} > 100 μM.

In the sequent research, a series of ether analogues with more metabolically stability were synthesized [74]. The most effective derivative **107** (CMB-087229) (Fig. 9) showed superior potency and *in vitro* pharmacological and pharmacokinetic features including protection against the mutant SOD1-induced cytotoxicity (ED_{50}: 67 nM), good performance in the evaluation of potassium channel (10 μM), protection of primary cortical neurons, Caco-2 permeability, rat liver microsomes and cytochrome P450 isozymes. Moreover, *in vivo* for its efficacy in an ALS mouse model, pharmacokinetic profile and brain penetration were investigated as well, compound **107** (1.0, 10, and 20 mg/kg) dose-dependently extended the survival of SOD1 G93A mice at the dose of 300 mg/kg. In addition, compound **107** exhibited favorable blood-brain barrier penetration effect. SAR research revealed that the size and electronics were imperative features at the meta-positions of the derivatives, the potency of analogues reduced in the sequence: Cl > CF_3 > F > Br > Ph.

3.3.4. Anti-Alzheimer's agents

Based on the structure of leading compound edaravone, Tok and co-workers [75] synthesized a cluster of analogues and investigated the potential anti-Alzheimer activity. Among the analogues, compounds **108** and **109** (Fig. 9) exerted most potent inhibitory effects, with the detail data listed in the Table 9. For the instance of the most potent AChE inhibiting agent **108** and MAO-B inhibiting agent **109**, the initial SAR could be summarized as that the variation of substituent groups strongly affected the inhibitory potency of analogues. Basic nitrogen atom in substituent groups of **108** significantly promoted the AChE inhibitory activity. In addition, incorporation of EWG increased the MAO-B inhibitory activity of **109**. It can be seen from the docking analysis that compound **108** was prepared with similar size with donepezil (Fig 10), and the room of cyclopentanone ring can be occupied by pyrazolone ring, providing the evidence of the activity and the idea to capture Alzheimer disease.

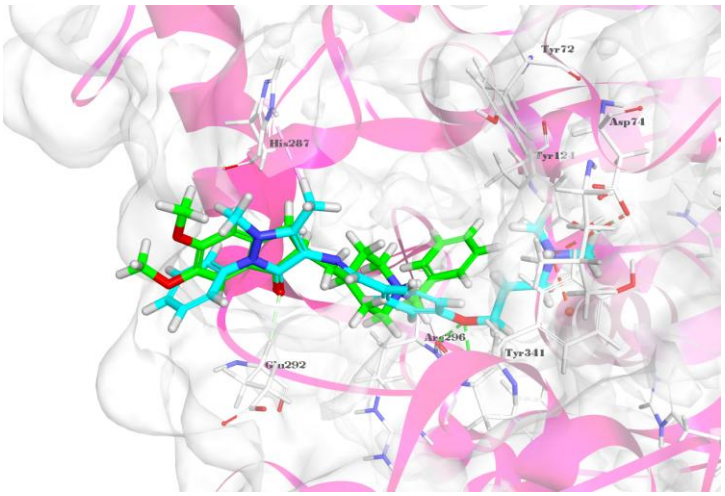


Figure 10. Ligand-protein interactions of compound **108** (blue) and donepezil (green) with AChE (PDB ID: 4EY7) accomplished by Discovery Studio 2019.

Table 9. Inhibition ratio of **108** and **109** on Alzheimer's enzymes.

Com.	**AChE IC_{50} (nM)**	**BChE inhibition % (10^{-3} M)**	**MAO-A inhibition %**	**MAO-B IC_{50} (nM)**
Donepezil	29	94.1	-	-
108	57	96.3	42.3	-
109	-	35.3	38.1	49

3.3.5. Other CNS target agents

A major inhibitory neurotransmitter in the mammalian brain is GABA that delivers primarily through the $GABA_A$ receptors [76]. $GABA_A$ receptors are considered to be heteropentameric transmembrane glycoprotein spanning both extracellular and intracellular regions [77]. Inspired from the pyrazolone-based precursors **110-112** (Fig. 9), Hintermann and co-workers [78] synthesized several analogues as the ligands for the benzodiazepine binding site of the $GABA_A$ receptor. Among them, compound **113** (Fig. 9) was the typical compound with the affinity of IC_{50} values of α1 $GABA_A$ receptor, α2 $GABA_A$ receptor, α1 $GABA_A$ BZ receptor, α2 $GABA_A$ BZ receptor for 49, 271, 46 and 271 nM, respectively, however, the weak activity of compound **113** was observed in anxiety models *in vivo*, which was suspected due to the high level of clearance (*in vitro*: CL_{int} rat: 128.3 μL/min∗mg). SAR study suggested that the 2-Cl-benzyl substituent group was initially maintained for the purpose to investigate the influence of core modifications, variations of substituent groups on the aromatic pyrazolone moiety leading to the mixed results. The corresponding analogues were very weak agonists at α2 and some behaved as antagonists at α1.

Glycogen synthase kinase 3 (GSK-3), a regulator of glycogen metabolism, has been well known to be involved in a variety of intracellular signaling, and a lot of GSK-3 inhibitors has been used for the treatment of CNS disorders including Alzheimer's disease (AD) [79], Parkinson's disease [80], stroke, traumatic brain injury, and bipolar disorders [81]. Pyrazolone derivatives were chronicled to show

activity on this target as well [82], the most promising compound **114** (Fig. 9) inhibited GSK-3 with IC_{50} value of 34 nM. Further investigation demonstrated that this compound possessed good kinase selectivity, and protective effects in oxidative stress mode in neuronal cell and locomotor hyperactivity in C57BL/6J mice were observed. SAR investigation indicated that non-substitution on the A ring was advantageous for the activity because only compound **114** exhibited the pronounced inhibitory effect among the synthetic compounds. Interestingly, the known GSK-3 inhibitors i.e. bisindol-maleimides (**115**) [83] and hymenialdisine (**116**) [84] (Fig. 9) contain the moieties structurally similar to the pyrazolone scaffold, which indicated the reasonability of using pyrazolone for the design of the GSK-3 inhibitor.

According to the structure of (*S*)-α-aminoadipic acid, which was a activating agent of important functional excitatory amino acid receptor mGlu2 and mGlu6 subtypes, compounds **117** and **118** (Fig. 9) were synthesized by Zimmermann et al. [85] thought some reactions. However, no significant agonist or antagonist activity from test compounds at the $mGlu_{1a}$, $mGlu_2$, $mGlu_{4a}$, or $mGlu_6$ subtypes were observed at the dose of 1 mM, the inappropriate pK_a of analogues was considered as the potential reason of obstruct interaction of substituted groups with appropriate sites at the receptors.

3.4. Anti-inflammatory agents

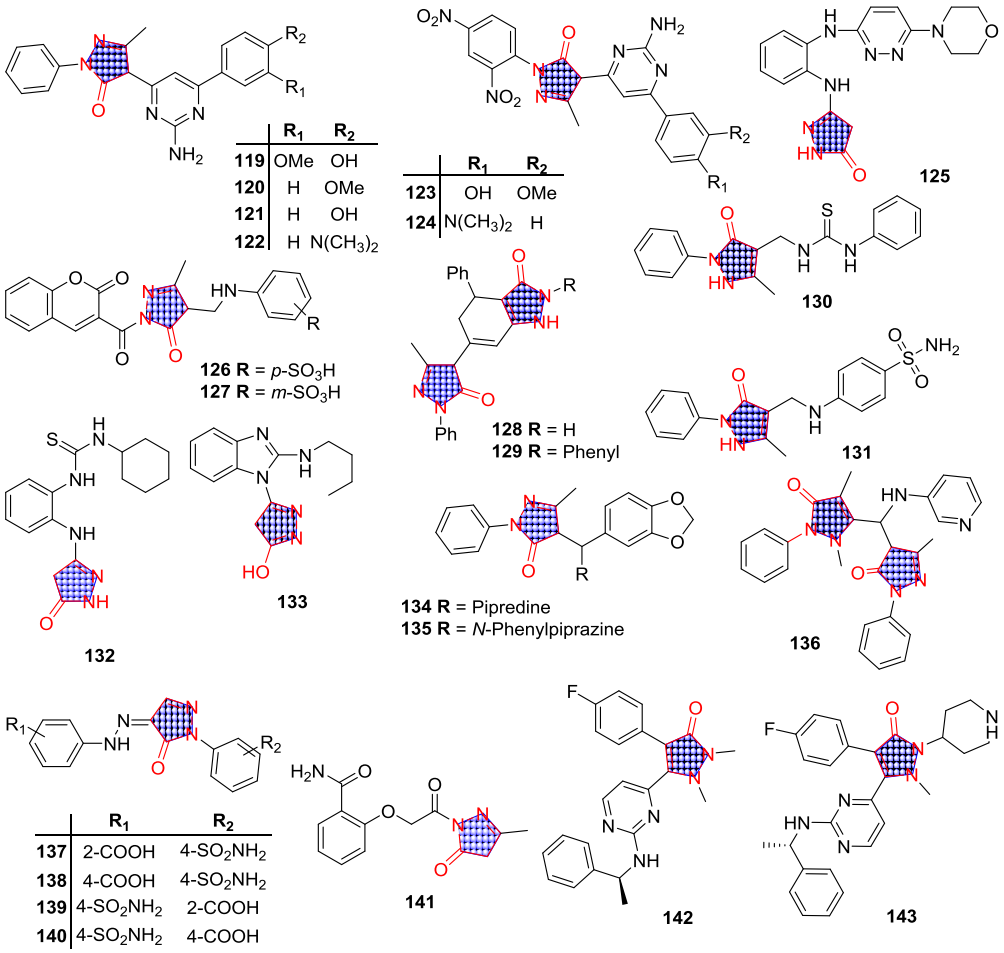


Figure 11. Pyrazolone derivatives with anti-inflammatory activity.

More than 100 years of synthetic work have resulted in three privileged pyrazolones derivatives with anti-inflammatory potency, namely antipyrine, propyphenazone and metamizol which are still widely used [86]. The structure characteristic that methyl groups attach to the ring nitrogen atoms to enhance the activity has been retained from antipyrine to newly reported analogues. Based on the structure of marketed anti-inflammatory drugs including antipyrine and aminophenazone, several pyrazolone derivatives have been designed and synthesized as anti-inflammatory agents.

With the thorough understand of inflammatory reactions, using single mice or rat model to evaluate the analgesic effect gradually fall short of demand to investigate the

activity, more and more targets are involved into the determination including COX-1, COX-2, 5-LOX, TNF-α, etc. Pyrazolones with anti-inflammatory effects tend to inhibited the activities of COXs and LOXs, which catalyze the conversion of arachidonic acid into prostaglandins or leukotrienes, meanwhile, phosphatase inhibitory of pyrazolones have also been disclosed [87], indicating the potential of pyrazolone motif in this field. The structural similarity between pyrazolone and COX-2 selective inhibitor celecoxib also provides possibility to develop them into potential clinical candidates [88-91]. The gastrointestinal side effects existing in the usage of COX-1 inhibitors and the cardiovascular side effects in COX-2 inhibitors suggest researchers to consider the inhibitory potency of anti-inflammatory agents on both COX-1 and COX-2, the story of the development of imrecoxib and the conception of moderate selectivity for COX-2 enzyme have been reported as references [19]. It can be seen from the binding affinity models of celecoxib and pyrazolone derivative **131** with COX-1 and COX-2 (Fig. 12) that pyrazolone group maintain the similar pi-alkyl effect with electron group of alkyl groups in the pocket residues compared to pyrrazole ring because of its property similar to aromatic ring. The carbonyl group in pyrrazole is a favorable hydrogen acceptor which is feasible to form potential H-bond with alkaline amino acids like arginine, lysine and histidine, meanwhile, the amino group is a hydrogen donor easy to form hydrogen bond with residues like glutamine (Fig. 12D).

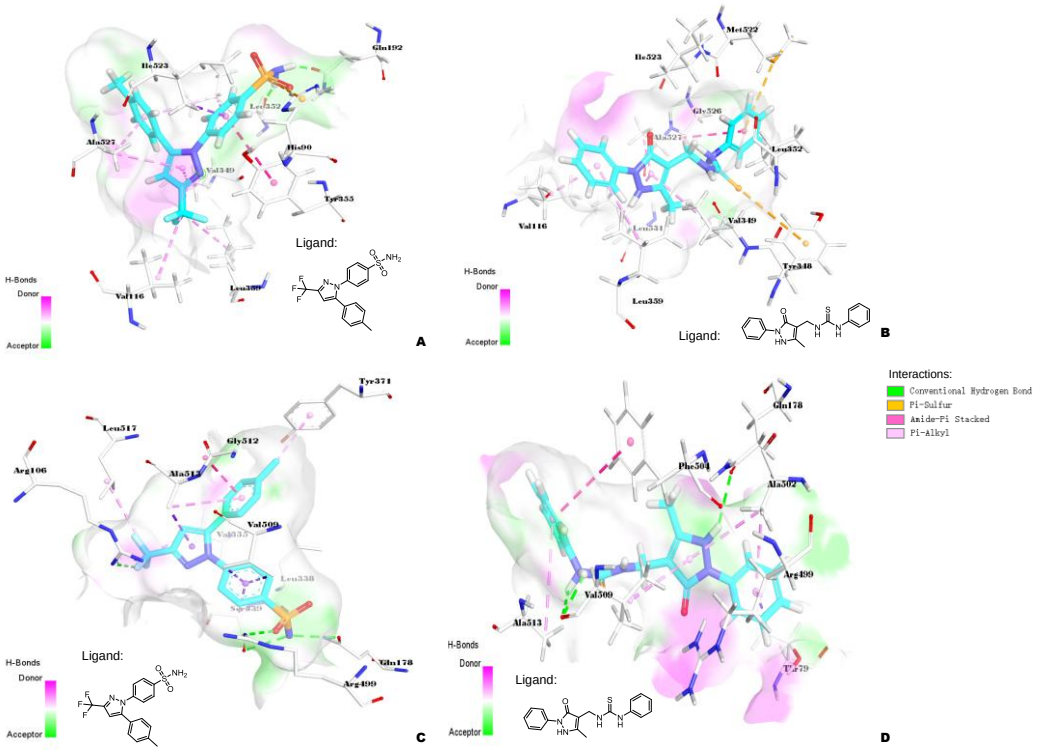


Figure 12. Ligand-protein interactions of celecoxib (**A**) and pyrazolone derivative **131** (**B**) with the active site of COX-1 (PDB ID: 3KK6), celecoxib (**C**) and pyrazolone derivative **131** (**D**) with the active site of COX-2 (PDB ID: SLN1) accomplished by Discovery Studio 2019.

A cluster of pyrazolone and amino pyrimidine derivatives **119**-**124** (Fig. 11) were synthesized by Antre and co-workers [92], with obvious anti-inflammatory potency in carrageenan-induced rat paw edema model (Table 10). In regard to SAR, in contrast to the substitution of chlorine and nitro, the anti-inflammatory effects of these analogues were significantly promoted when the electron-donating groups of C-6 aminopyrimidine benzene ring were hydroxyl, methoxy and dimethylamine.

Table 10. Result of anti-inflammatory activity of the tested derivatives.

Com.	IC_{50} (μM)		Selectivity index	Anti-inflammatory activity
	COX-1	COX-2	(SI)	(% inhibition)
119	-	-	-	61.23
120	-	-	-	61.02
121	-	-	-	61.84
122	-	-	-	62.00
123	-	-	-	62.51
124	-	-	-	62.05
125	2.86	0.39	7.36	62.30

126	-	-	-	77.88
127	-	-	-	79.91
128	-	-	-	56.2
129	-	-	-	55.2
130	80	0.20	400	91.00
131	>100	1.00	>100	92.00
132	13.40×10^{-5}	2.83×10^{-5}	4.73	56.00
133	22.72×10^{-5}	4.69×10^{-5}	4.84	61.00
134	1.60		0.98	80.00
135	1.57		0.91	98.00
136	1.74		0.99	89.20
137	4.08	0.77	5.29	-
138	3.81	0.72	5.29	72. 72
139	3.76	0.66	5.69	-
140	-	-	-	72.72

Nadia and colleagues [93] synthesized multiple pyrazolone-pyridazine conjugates and screened their anti-inflammatory activity *in vivo* and *in vitro*. Compound **125** (Fig. 11) exhibited the strongest anti-inflammatory activity in the test of carrageenan-induced mice paw edema model and in COX-1 and COX-2 inhibition test (Table 10). It also inhibited the production of inflammatory cytokines including TNF-α and IL-6 in serum. SAR study showed that the replacement with bulky aliphatic secondary amines such as morpholine exerted good anti-inflammatory effects.

Mannich base derivatives **126** and **127** (0.03 mmol/kg) (Fig. 11) displayed the remarkable anti-inflammatory effect on the carrageenan-induced acute albino rats paw edema model with inhibitory rates of 77.88% and 79.91%, respectively, after 6 h of administration [94]. The preliminary SAR demonstrated that analogues containing EWGs in the Mannich base phenyl ring at position 4, especially sulfonic group enhanced the activity.

Abbady and co-workers synthesized some new pyridines, pyrans, and indazoles

with pyrazolone ring [95]. Among the synthetic products, indazole derivatives **128** and **129** (10 mg/kg) (Fig. 11) obviously suppressed swelling of in rat hind paws induced 5 h after injection of carrageenan, with inflammatory inhibition rates of 56.20% and 55.20%, respectively, indicating excellent anti-inflammatory activity.

A series of 5-methyl-2-phenyl-1H-pyrazol-3 (2H)-one analogues were prepared and determined for their anti-inflammatory effects [96]. The outcome showed that the derivatives **130** and **131** (Fig. 11) were proved to have superior inhibitory potency against both the targets of inflammation COX-1 and COX-2 (Table 10). Furthermore, derivatives **130** and **131** also exhibited favorable anti-inflammatory effect in carrageenan induced rats paw edema model with ED_{50} values of 102 and 109 mg/kg *in vivo*, respectively. Regarding SAR, pyrazolones containing C-3 methyl group, C-4 urea substitution and carbonyl at 5-position posed an impact on COX enzymes inhibition. The substituent with urea-phenyl group at 3-phenyl ring was more active than that containing chlorine at the same position and unsubstituted urea. Moreover, thiourea derivatives imparted strengthen activity compared with those with urea and guanidine.

Ashraf et al. [97] successfully prepared two series of pyrazolone analogues and tested their anti-inflammatory effect *in vivo* and *in vitro*. The derivative **132** and the enolate**133** (Fig. 11) displayed excellent inhibitory activity on COX-2 (Table 10) as well as potent edema inhibition. SAR investigation showed that these compounds with unsaturated moiety such as the allyl and aryl groups maintained stronger activities than those with alkyl groups. Thiourea analogues **132** also improved

anti-inflammatory potency in the presence of the bulky hydrophobic cyclohexyl group.

El Sayed and colleagues designed and synthesized novel heterocyclic derivatives containing antipyrine and pyrazolone framework [98]. The pharmacology tests result revealed that derivatives **134-136** (Fig. 11) exhibited significant anti-inflammatory activities in different degree both *in vivo* and *in vitro* (Table 10). The SAR study indicated that the presence of the 3-benzo[d][1,3]dioxole ring system and the *N*-containing heterocyclic amine attached to the methyl group at 4-position of the antipyrine structure was very essential for activity as in case of compounds **134** and **135**.

A cluster of novel pyrazolone analogues containing aminosulfonyl group were synthesized and investigated for the anti-inflammatory potency [99]. The outcome showed that three compounds **137-139** (Fig. 11), as potent anti-inflammatory agents, exerted strong inhibitory effects against both COX-2 (Table 10) and 5-LOX (IC_{50}: 0.53, 0.52 and 0.57 μM in order) with superior COX-2 SI values. Compounds **138** and **140** remarkably diminished rat paw edema induced by carrageenan with ED_{50} values of 0.044 and 0.079 mmol/kg, respectively, exhibiting excellent anti-inflammatory activity *in vivo*. In terms of SAR study, the replacement of 2-carbonyl group in the derivatives with SO_2NH_2 as the main active group promoted activity.

Fahmy et al. [100] tested anti-inflammatory effects of several novel *O*-substituted salicylamides. Among all analogues, pyrazolone derivative **141** (Fig. 11) exhibited moderate anti-inflammatory activity in carrageenan-induced oedema model. The

multiple bioactivity test results indicated the pyrazolone and the structurally similar group pyrazole could be the potential substitutions.

Golebiowski and co-workers synthesized some novel monocyclic pyrazolone and investigated their inhibition on the inflammatory cytokines [101]. The outcome showed that compound **142** (Fig. 11) significantly reduced the expression of TNF-α induced by lipopolysaccharide (LPS) with IC_{50} value of 13 nM. Furthermore, through SAR study, it can be found that benzyl amino substituents were more active than those of aminopyridine ring, and *N*-methyl substitution on the pyrazolone was more effective than ethyl substitution. Currently, the topic of inflammatory reaction has beyond the analgesic agents, immunoreactivity targets also involved. The author observed the interactions of p38 kinase with another potential synthesized pyrazolone derivative **143** (Fig. 13), in which the piperidine ring was introduced to gain the better pharmacokinetic parameters. The carbonyl group of pyrazolone ring was proved to form the H-bond with the amine group of Lys 53, revealing the importance of pyrazolone moiety of this type of inhibiotor.

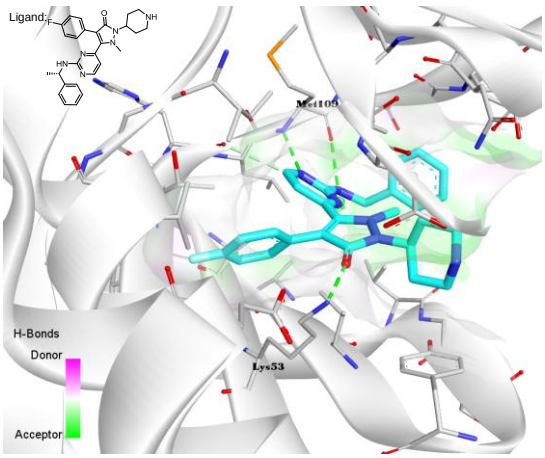


Figure 13. Resolved pharmaceutical cocrystal of pyrazolone derivative **143** with p38 kinase (PDB: 1YWR).

3.5. Antioxidant agents

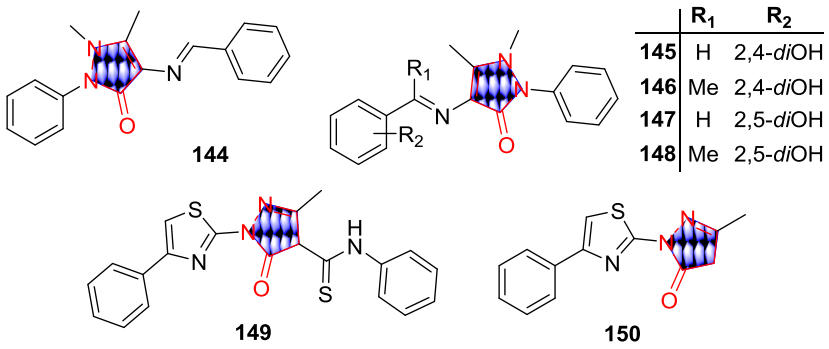


Figure 14. Antioxidant of pyrazolone derivatives.

Free radicals, known to be highly reactive molecules resulted *via* different biochemical reactions in the body. These free radicals lead the other metabolites to be oxidized and caused different diseases due to oxidative stress [102]. Pyrazolones played a role in antioxidant activity, referring to the antioxidant mechanism of edaravone, C=C double bond formed by the action of tautomerism of carbonyl group on pyrazolone was considered to be important [103]. In the light of the structure motif of 4-aminoantipyrine, Schiff base derivative **144** (Fig. 14) was prepared and determined for the antioxidant activity [104]. The derivative **144** exerted a strong antioxidant effect with IC_{50} value of 31.26 µM. As a non-phenolic antioxidant agent, the antioxidant effect of compound **144** was considered to be relative to the formation of proton free radicals by the C-7 or C-11 methyl groups. The Schiff base pyrazolone analogues were also synthesized by Khan et al. [105], among the products, phenol productions **145-148** (Fig. 14) exhibited significant antioxidant effect in DPPH test with the IC_{50} values of 20.14, 19.12, 17.14, 15.16 µM, respectively, which was even stronger than the standard drug n-propyl gallate (IC_{50}: 30.27 µM). SAR study revealed that double phenol group substituted analogues performed better than other moieties because of the reducibility of phenolic hydroxyl group, and 2.5-*di*OH

substitution was stronger than 2,4-*di*OH.

Gaffer and co-workers [106] screened the antioxidant activity of a cluster of thiazolyl-pyrazolone derivatives through 2, 2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical cation decolorization assay. Compounds **149** and **150** (Fig. 14) (2 mM) exhibited the strongest antioxidant potency with the inhibition of 88.6% and 85.7%, respectively. Thereinto, compound **149** exhibited better activity than standard inhibitor ascorbic acid (inhibition: 88.20%). SAR investigation was concluded as that the presence of benzene on the thiazole ring and phenylthiocarbamoyl moiety along with core pyrazolone group was benefit to the antioxidant effect. Additionally, 4-phenyl substituent group on the thiazole ring was better than the methyl substitution.

3.6. Anti-tuberculosis agents

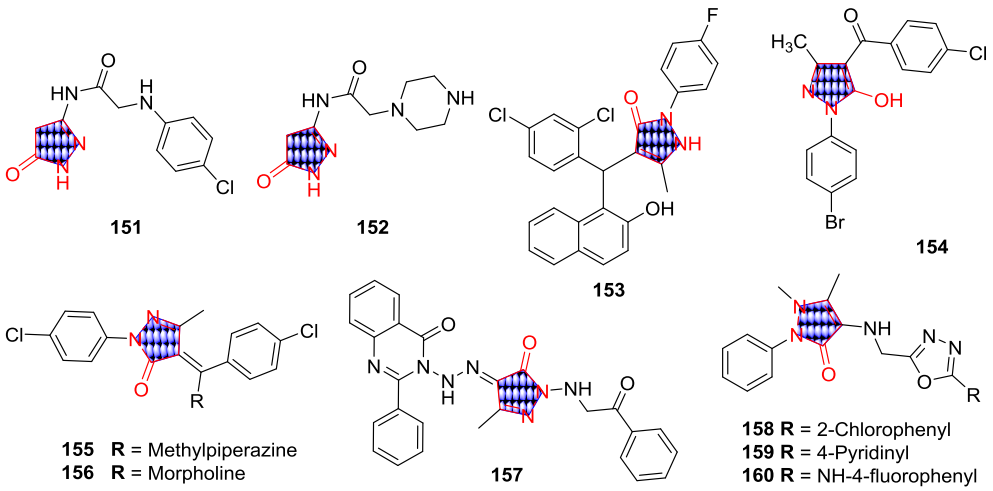


Figure 15. Pyrazolones with antitubercular activity.

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis* (MTB) and embodies one of the leading causes of death around the world [107]. The dangerous spread of TB is primarily because of its association with HIV infection and to the rapid development of multidrug-resistant (MDR) strains of

MTB [108]. Pyrazolone as the precursor has been reported to show potential antitubercular activity.

Table 11. Antitubercular properties of the designed compounds.

Com.	MTB MIC (μg/mL)	IC_{50} (μM)	Selectivity index (SI)
151	-	<0.37	633.35
152	-	<0.44	630.75
153	0.79	-	-
154	4.00	-	-
155	4.00	-	-
156	4.00	-	-
157	3.11	-	26.35
158	1.97	-	-
159	0.78	-	-
160	0.78	-	-

Sivakumar et al. [109] prepared two series of hybridized pyrazolone analogues and determined their antitubercular effect. The most potent compounds **151** and **152** (Fig. 15) possessed apparent antitubercular effects (IC_{50} < 0.1 μg/mL). Furthermore, SAR investigation indicated that the antitubercular activity of the compounds was markedly improved in the absence of double bond in the imine side chain and the benzene ring at the end of pyrazolone moiety.

Pethaiah et al. [110] synthesized several 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolone analogues in water through one-pot process and investigated the antitubercular activity against MTB *in vitro*. The MIC value of potential compound **153** (Table 11) (Fig. 15) was better than clinical drugs. SAR showed that the replacement on the *N*-aryl ring of derivatives contributed antimycobacterial activity. Specifically, the analogues containing electron-withdrawing groups with halogens and nitro groups showed stronger activity

compare with aryl rings containing electron-donating groups such as methoxide, methyl and isopropyl.

Daniele et al. [111] prepared various pyrazole analogues and evaluated their antitubercular activities against *M. tuberculosis*. Compound **154** (Fig. 15) was the most potent candidate (Table 11). SAR study demonstrated that the halogens on phenyl ring and the methyl group at third position of pyrazole ring showed higher antitubercular effect than that contained alkyl in the same position.

Two series of new pyrazolone analogues were prepared and assessed for the anti-MTB activity [112]. Two analogues **155** and **156** (Fig. 15), containing the *p*-chlorophenyl ring, were regarded as the most promising MTB inhibitors (Table 11). Meanwhile, the presence of *N*-methyl-piperazine and morpholine groups remarkedly improved anti-MTB effects.

Several Mannich bases and Schiff bases of pyrazolone framework were synthesized [113]. The results showed that analogue **157** (Fig. 15) could be used as a potential antitubercular drug due to its extremely high activity (Table 11) over that of the standards ethambutol and ciprofloxacin. SAR study revealed that derivatives with acyl substituent had better anti-MTB ability than those comprising EWGs such as nitro, chlorine, and carboxyl and electron donating group including hydroxyl.

Ahsan and co-workers [114] designed some diversified pyrazolone derivatives aiming at MTB and isoniazid resistant MTB, among which compounds **158** and **159** (Fig. 15) exhibited pronounced inhibitory effect (Table 11), the outstanding inhibitory effect of **159** against isoniazid resistant MTB strain was observed as well and the

compound **158** was revealed to show strong antibacterial effect simultaneously. SAR study revealed that *N*-aryl with electronegative substituent group showed strongest antitubercular potency, in which 4-pyridinyl group had maximum inhibition, compared to 2-chlorophenyl, 4-chlorophenyl and 4-aminophenyl group substitution. The electron donating group such as 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl and 4-methylphenyl exhibited less inhibition. In the follow up research[115], the potent compound **160** (Fig. 15) was selected from the novel synthesized analogues with excellent activity and free from cytotoxicity (> 62.5 μg/mL) appeared. Better drug-likeness was obtained after adding the imine group between the oxadiazol and the phenyl ring and SAR was summarized as that EWGs produced more inhibitory effect.

3.7. Antiviral agents

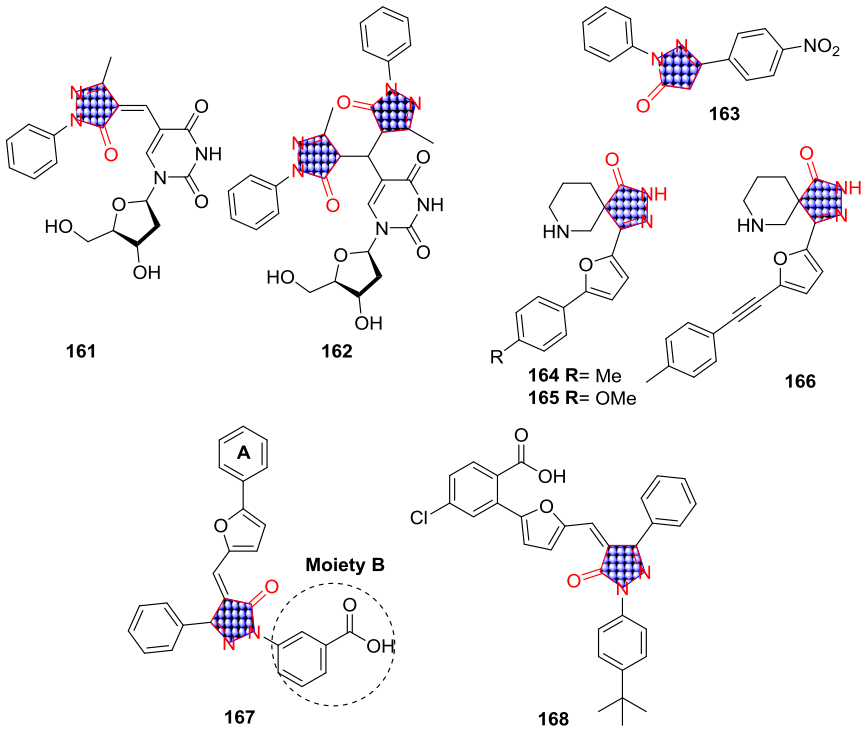


Figure 16. Antiviral of pyrazolone analogues.

Multiple viruses widely exist in the nature and threaten public health[116].

Pyrazolone has been used to generate antiviral agents, involving in anti-orthopoxvirus, anti-protease-resistant prion protein (PrP-res), anti-severe acute respiratory syndrome (SARS) and anti-buffalopox virus (BPXV) agents.

Fan et al. [117] synthesized a series of pyrimidine-pyrazolone nucleoside chimera analogues and determined the anti-orthopoxvirus activity *in vitro*. The consequence proved that compounds **161** and **162** (Fig. 16) exerted the most potent anti-orthopoxvirus effect (Table 12). SAR study revealed that the activity was enhanced after matching with the pyrazolone moiety.

Table 12. Inhibition of orthopoxvirus replication by pyrazolo-pyrimidine nucleosides

Com.	EC_{50} (μM)				Toxicity CC_{50} (μM) Neutral red uptake
	Vacciniad CPE	Vacciniad PR	Cowpox CPE	Cowpox PR	
Cidofovir	3.2	20	7.1	32	>317
161	1.7	6.9	0.3	5.6	>286
162	20	11	1.8	9.0	>292

Note: CPE-reduce viral cytopathogenicity, PR-plaque formation.

In 2007, Kimata and co-workers [118] reported the synthesis and assessment of multiple PrP-res accumulation inhibitors according to the structure of edaravone, in which the most potent compound **163** (Fig. 16) displayed PrP-res inhibitory effect in the ScN2a cells with IC_{50} value of 3 nM, which was 130 times more active than quinacrine and more than 300-fold effective than edaravone. Furthermore, no significant SOD (superoxide dismutase)-like activity was observed, indicating potential novel mechanism of the PrP-res inhibitory effect. SAR study demonstrated that the position and class of substitutions were not directly related to the potency of suppressing the accumulation of PrP-res but substituted the nucleus with 1-cyclohexyl, 3-isopropenyl, 3-(4-nitrophenyl) and 4-benzoyl could enhance the inhibitory activity.

Srinivasan and teammates [119] synthesized several spiro-piperidinyl pyrazolone derivatives inspired from the skeleton of spiramide and assessed their antiviral properties against *Buffalopox* caused by BPXV on Vero cells *in vitro*. The results suggested that derivatives **164**, **165** and **166** (Fig. 16) were the most potent analogues with electron donating groups on the aromatic ring.

Kumar and coworkers [120] synthesized multiple pyrazolone analogues as SARS-coronavirus (CoV) and Middle East Respiratory Syndrome (MERS)-CoV 3C-like protease inhibitors, among which compounds **167** and **168** (Fig. 16) exerted the strongest inhibitory effects against SARS and MERS with IC_{50} values of 6.4 and 5.8 μM (**167**), 5.8 and 7.4 μM (**168**), respectively. SAR study revealed that the carboxylate group is a crucial pharmacophore and its presence either at the C-2 position of ring A or moiety B is critical for the activity, meanwhile, the chlorine at C-5 position of ring A slightly decreases the activity. It can be seen from the docking studies that pyrazolone group in both compounds **167** and **168** played important roles to form H-bonds with residues Glu 166 and His 41 in SARS $3CL^{pro}$, respectively.

3.8. Lipid-lowering agents

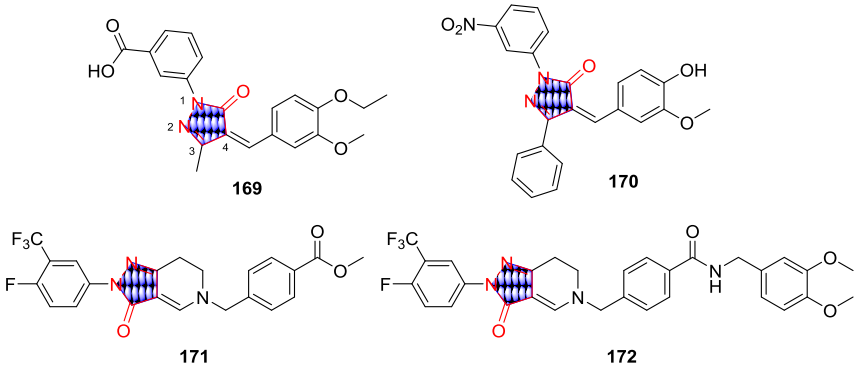


Figure 17. Pyrazolones as lipid-lowering agents.

With the change of people's lifestyle and dietary structure, the incidence of fatty

liver is increasingly high. In particular, non-alcoholic fatty liver disease (NAFLD) has seriously endangered people's life and health [121]. However, due to the complex pathogenesis [122], it is often neglected in clinical practice. Pyrazolinone derivatives can reduce cholesterol and lipid accumulation in the body by regulating multiple indicators, such as AMPK and FXR. Therefore, it is of importance to improve the lipid-lowering activity by modifying the structure of pyrazolone. The pyrazolone derivatives are also reported to be the selective antagonists to the nonsteroidal farnesoid X receptor (FXR) [123], which maintains the bile acid homeostasis and plays crucial roles in the control of cholesterol, lipid, and glucose metabolism [124, 125]. Based on the screen of the known FXR modulators, the lead compound **169** (Fig. 17) (IC_{50}: 69.01 μM) was identified with the help of homogeneous time-resolved fluorescence (HTRF) assay. On the basis of **169**, further modification was carried out accordingly. The most promising compound **170** (IC_{50}: 8.96 μM) displayed antagonistic capability 10-fold and 8-fold higher than that of the control *Z*-guggulsterone and the original analogue **169**, respectively. Compound **170** was further proved to interact with FXRαLBD with high binding affinity, and potent antagonistic activity against FXR in two cell testing platforms. In addition, compound **170** strongly inhibited the regulating activities of chenodeoxycholic acid on FXR target genes. Furthermore, compound **170** was proved to play a role in lowering the contents of triglyceride and cholesterol in human hepatoma HepG2 cells and in the cholesterol-fed C57BL/6 mice. SAR can be interpreted that changes of substituents on the 1, 3, and 4-positions of pyrazolone group had crucial influence on antagonistic

effect, and appropriate structural optimizations on the above regions can substantially strengthen activity.

NAFLD is a clinical syndrome identified by hepatic steatosis. It is closely linked to obesity, insulin resistance and dyslipidemia. AMP-activated protein kinase (AMPK) functions as an energy sensor and plays an important role in regulating lipid metabolism [126, 127]. According to the structure of lead compound **171** (Fig. 17), Zhang et al. [128] synthesized multiple pyrazolone derivatives as AMPK activators to suppress lipid synthesis and reduce lipid accumulation in *ob/ob* mice. The most potent compound **172** directly activated the kinase domain of AMPK with an EC_{50} value of 2.1-0.2 μmol/L and acted as a non-selective activator of AMPK complexes, additionally, compound **172** suppressed the accumulation of triglyceride in HepG2 cells dose-dependently. The outcome demonstrated that the AMPK activators could be part of a treating method for NAFLD and related metabolic disorders.

3.9. Antihyperglycemic agents

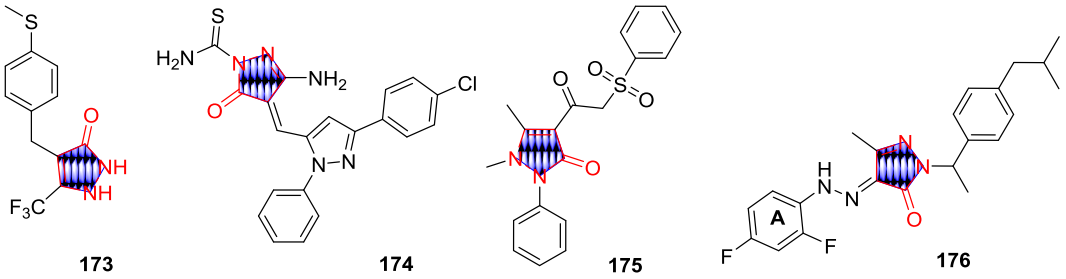


Figure 18. Pyrazolones as antihyperglycemic agents.

Diabetes is considered to be relative to overindulgent life-style and thus is thought as major health concern in industrialized countries [129]. Pyrazolones have been disclosed to be antihyperglycemic through multiple targets including aldose reductase (AR), α-glucosidase and α-amylase. The antihyperglycemic activity of

pyrazolone derivatives was explored by Kees et al. [130] The potent compound **173** (100 mg/kg) (Fig. 18) caused a 68% decrease in plasma glucose in *db/db* mice, moreover, it essentially normalized the level of glucose at 20 mg/kg (57% reduction) and maintained remarkable reduction at 2 mg/kg (30% decrease). SAR could be concluded that the substitution of 4-methylthio, methylsulfinyl, or ethyl to a benzyl group at C-4, in combination with trifluoromethyl at C-4 position of pyrazolone (hydroxy tautomer) formed potent antihyperglycemic agents in mice. In addition, the chemical "trapping" of four of the seven possible tautomeric forms of the heterocycle by *mono*- and dialkylation at the acidic hydrogens gave several additional potent analogs.

Kadam and co-workers [129] synthesized several pyrazolone derivatives as inhibitors of AR, in which compound **174** (Fig. 18) displayed the most promising inhibitory with IC_{50} value of 6.30 μM. In regard to SAR, it was possible to note that the hydrophobic groups like benzene ring with pyrazolone adversely influenced AR inhibition, while the introduction of carbothioamide group increased inhibitory effect. Because of the simultaneous existing of arbothioamide moiety and 3-(4I-methoxyphenyl)-1-phenyl-1H-pyrazole and 3-(4I-chlorophenyl)-1-phenyl-1H-pyrazole substituent group at first position of pyrazolone, compound **174** exerted the best activity. Docking analysis suggested that substituted groups of **174** gave the proper placement of hydrophobic groups in respective binding pockets of AR, avoiding the poor interactions because the size of substitutions was too small to occupy the binding pocket, and the pyrazolone moiety

in compound **174** was considered to play a role in form H-bond with the residue Cys 298.

Eldebss and colleagues [131] prepared a series of pyrazolones acting as α-glucosidase and α-amylase inhibitors, among which compound **175** (Fig. 18) exerted the most significant inhibitory effects with IC_{50} values of 14.67 and 63.66 μM, respectively. In the acute diabetic mice model, compound **175** reduced serum glucose level for the ratio of 32.16%, and in subacute study the ratio was 13.34% after administration for 2 h, which was even better than the effect of pioglitazone. The docking analysis indicated that the 1,5-dimethyl group of pyrazolone was important for the interaction between compound **175** and *α*-glucosidase, additionally, preserving the sulphone group was momentous to the inhibitory effect.

In 2014, Shetty et al. [132] synthesized multiple pyrazolone derivatives as *α* -amylase inhibitors. The consequence showed that compound **176** (Fig. 18) displayed the strongest inhibitory effect with the ratio of 61.6%. The primary SAR can be suspected as that introduction of disubstituted halogen analogues promoted the inhibitory effect due to its high electronegativity, moreover, multi-fluoro substitution on A ring could be the potential active group.

3.10. Protein inhibitors

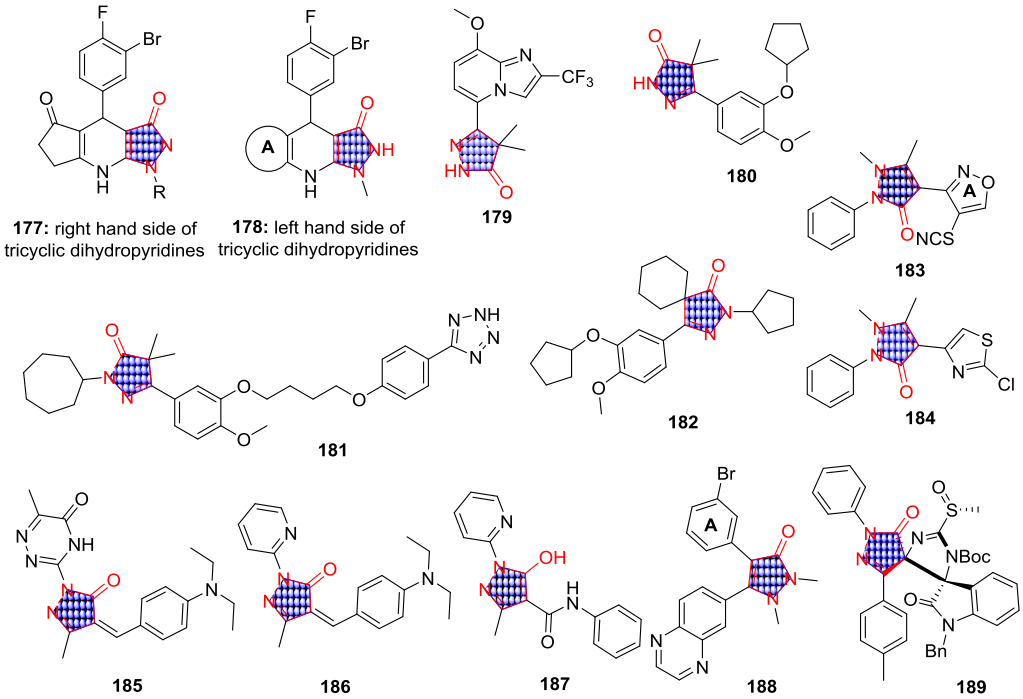


Figure 19. Pyrazolone as protein inhibitors.

In addition to the activities mentioned above, pyrazolones have been shown to inhibit the proteins including K_{ATP} channel protein, phosphodiesterase (PDE), aromatase, divalent metal transporter 1 (DMT1), human carboxylesterase1 (hCE1) and transforming growth factor (TGF) βR1, indicating the multiple targets therapeutic action and favorable drug-likeness of pyrazolone derivatives. Drizin and co-workers [133] designed and synthesized a cluster of pyrazolone derivatives as K_{ATP} channel openers inspired from disclosed compounds (the skeleton of **177** and **178**, Fig. 19), together with the investigation of SAR. It can be concluded that cyclopentanone in the left hand portion (A area) of the derivative was 4-fold more potent than cyclohexanone. The introduction of gem-dimethyl groups as well as incorporation of oxygen in the cyclohexanone ring in the left hand portion of the molecule elevated the potency 10-fold. In the right hand portion of the molecule, the activity was promoted 5-fold when the NH-group on the pyrazolone was replaced by oxygen atom.

Ochiai et al. [87] synthesized several 4,4-dimethylpyrazolone analogues as cyclic 30,50-nucleotide PDE 3/4-inhibitor, in which the compound **179** (Fig. 19) was demonstrated to be the most potent compound inhibiting PDE 3A and PDE 4B with the IC_{50} values of 0.14 and 0.15 μM, respectively. In addition, significant bronchodilatory activity was observed. SAR study demonstrated that the presence of pyrazolopyridine 7-substituent can engender potency for the inhibition of PDE 4, and the isosteric imidazopyridine substitution made for the pyrazolopyridine subunit increases the well-balanced dual of PDE 3 and PDE 4. As a member of PDEs, *Trypanosoma brucei* PDB1 (TbrPDEB1) was described as a crucial target for the therapy of Human African trypanosomiasis [134, 135], which was a parasitic disease caused by the protozoan pathogen *T. brucei*. Orrling and colleagues [136] explored catechol pyrazolinones as trypanocidals inspired from the structural motif rolipram. After the scaffold merging, the premier potent compound **180** (Fig. 19) was selected with the TbrPDEB1 IC_{50} value of 12 μM. Furthermore, with the help of homology modeling and docking studies to guide fragment growing into the parasite-specific P-pocket, which was a unique sub-pocket that extended from the invariant glutamine (Gln 874) through the protein to the solvent in the enzyme binding site, the fragment growing compound **181** (Fig. 19) was emerged with the outstanding activities for inhibiting *T. brucei rhodesiense* with IC_{50} value of 60 nM and TbrPDEB1 with IC_{50} value of 49 nM. SAR investigation elucidated that pyrazolone held a conjugated π-system and additional possibility to interact with aromatic residues in the binding pocket of TbrPDEB1. Moreover, the extended alkyl chain in the analogues of **181**

enabled to reach and enter the P-pocket, which displaced water from the length of the P-pocket and placed the tetrazole at the solvent-exposed exit of the pore. The tetrazole in compound **181** formed a H-bond with Tyr 845, further stabilizing the conformation. Afterwards, according to the structure of **180** and **181**, Amata and co-workers [137] designed and synthesized a cluster of derivatives, while poor inhibitory effect was detected, the most promising pyrazolone compound **182** (Fig. 19) only showed inhibition for 18% at the dose of 10 μM, indicating a better understanding of the subtle structural features was necessary for an optimal enzyme inhibition.

Yi and co-workers [138] synthesized the diversified pyrazolone derivatives and screened the aromatase inhibition effect. The most active compounds were **183** and **184** (Fig. 19), showing IC_{50} values of 2.3 nM and 3.3 nM, respectively. The inhibition of compound **183** was even stronger than the reference letrozole (IC_{50}: 2.8 nM). SAR analysis indicated that the pyrazolone moiety could inhibit aromatase by binding to its active site. The bioactivity result proved that the presence of substitutions in compounds **183** and **184** were good for the inhibition, as for the most promising compound **183**, the cyano group was revealed to interact with the important residues Arg 115 and Met 374 of the aromatase.

From the high-throughput screening of DMT1 [139], pyrazolone hit **185** (IC_{50}: 2.57 μM, Fig. 19) was elaborated as the structural motif. Preliminary hit-to-lead efforts gave the pyridyl analog **186** (IC_{50}: 1.53 μM), which imparted several undesirable features including most notably an extended conjugation motif affording an intense orange color as well as Michael acceptor features at the benzylidene

α-carbon. Further investigation introduced more substitutions to modify these skeletons, and the most promising compound **187** (IC_{50}: 0.64 μM) was distinguished because of its eminent absorption, distribution, metabolism and excretion (ADME) properties, the inhibition of CYP3A4 was significantly reduced and the rat microsome metabolic stability was markedly hoisted compared to the precursor **186**. SAR of the analogues of **187** implied that EWGs on the benzene ring were slightly preferred over electron-donating ones.

Based on the existing TGFβR1 inhibitors, Guckian and colleagues [140] described a series of TGFβR1 kinase inhibitors including a pyrazolone group which allowed replacement of the ubiquitous nitrogen H-bond acceptor within the core with a carbonyl without remarkable loss in biochemical activity. The most active compound **188** (Fig. 19) inhibited the TGFβR1 kinase with the Ki value of 0.012 μM and suppressed the PAI-Luc with the IC_{50} value of 0.22 μM. SAR can be recapitulated that the carbonyl moiety of pyrazolone was potent to capture the H-bonding interaction with the key residue Lys 232 of TGF*β*R1. The A ring was the area the authors paid attention to modify, and they found that when A ring was substituted as pyridine ring could elevate the activity because it contained a basic nitrogen in the 2-position to occupy the hydrophobic pocket. As for the aromatics on A ring, substitutions on *meta* position was proved to be superior to *ortho* or *para* position, and this position was very sensitive to the nature of substitution with preference for small hydrophobic substituent groups without branching on the α-carbon, considering to influence of the size of substituted atom on the hydrophobic pocket, bromo group

was selected for the suitable substitution for further investigation.

Asymmetric synthesis asymmetric spiro-pyrazolone derivatives have been a hotspot in recent years, while the investigations of bioactivity about these productions and the relationships between their enantioisomerism and activity are still rare. Bao et al. [141] synthesized a series of dispirotriheterocyclic scaffold derivatives and screened the inhibitory effects against hCE1. It is worth noting that the most potent compound **189** (Fig. 19), in which there were two chiral centers important for inhibitory potency, exerted the strong inhibition with IC_{50} value of 0.39 μM, whose activity was 20-fold stronger than its enantiomer, indicating the importance of asymmetric [3 + 2] cyclization process.

4. Conclusion and perspective

Pyrazolone core is one of the most explored precursors among diverse fused heterocycles, capable of multiple roles in different pathophysiological conditions. According to the concept of generalized bioisosteres [142, 143], as a typical synthetic rather than natural motif in medicinal chemistry, pyrazolone is potential to replace multiple moieties with similar chemical structure and bioactivities including parazole, imidazolin-5-one and 2,4-dihydro-1,2,4-triazol-3-one, etc., providing an important scaffold for drug development. Being a versatile molecule with immense biological significance, pyrazolone derivatives are being developed for several pathological screening including antimicrobial, antitumor, CNS effect, anti-inflammatory, antioxidant, antitubercular, antiviral and protein inhibitors activities since long.

The development of pyrazolone derivatives can be regarded as the epitome of medicinal chemistry, starting from antipyrine, several analogues have been explored and the precursor designing methods have evolved from structural modification to Fragment Based Drug Design and high-throughput screening simultaneously. With the development of science, machine learning, virtual screening and combinatorial chemistry technologies shorten the time of filtrating the leading compounds and will play a more and more important role in drug design in the future [144, 145]. Investigations for privileged scaffold from the perspective of SAR have been lasting several years [146-151]. It is probable that pyrazolone scaffold has its position in the establishment of compound library due to its good drug-likeness and broad bioactive properties. Moreover, as we mentioned in this article, the pyrazolone group maintains properties like aromatic and it is feasible to form pi-alkyl effect with residues in the potential target, and the carbonyl group in pyrrazole is a favorable hydrogen acceptor which is feasible to form potential H-bond, which provide evidence for the importance of pyrazolone structural motif in medicinal chemistry.

Pan Assay Interference Compounds studies consider that some poor drug-likeness compounds bring false positive results [152, 153], but pyrazolone is not on the list. Besides, the toxicity of pyrazolone derivatives is still alarming [154], because the loss and harm caused by the side effects of antipyrine and aminopyrine including leukopenia and agranulocytosis are still vivid. In this review, we have disclosed recent role of pyrazolones in the field of medicinal chemistry by discussing insights of SAR studies and binding conformations of these heterocycle compounds

with a variety of targets. These intelligences are helpful to explore novel pyrazolone analogues for the challenging pathophysiological conditions nowadays.

Abbreviations

A549: lung cancer cell lines; *ABTS*: 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid); *AChE*: acetylcholine; *AD*: Alzheimer's disease; *ADME*: absorption, distribution, metabolism and excretion; *ALS*: amyotrophic lateral scleorosis; *ALK*: anaplastic lymphoma kinase; *AMP*: Adenosine monophosphate; *AMPK*: AMP-activated protein kinase; *Arg*: arginine; *A. niger*: *Aspergillus niger*; *BPXV*: buffalopox virus; *BZ*: benzodiazepine; *Caco-2*: the human coloncarcinoma cell line; *C. albicans*: *Candida albicans*; *CLint*: clearance rate; *c-Met*: c-mesenchymal epithelial transition factor; *CNS*: central nervous system; *CoV*: coronavirus; *COX*: prostaglandin-endoperoxide synthase; *CYP3A4*: Cytochrome P4503A4; DMT1: divalent metal transporter 1; *DPPH*:

1,1-Diphenyl-2-picrylhydrazylradical2,2-Diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl;

EAC: Ehrlich ascites carcinoma cells; EC_{50}: half effective concentration; ED_{50}: median effective dose; *EDGs*: electron-donating groups; *EDTA*: ethylenediaminetetraacetic acid; *EWGs*: electron withdrawing groups; *FDA*: Food and Drug Administration; *FXR*: farnesoid X receptor; $GABA_A$: Gamma-Amino Butyric Acid-A; *G. candidum*: *Geotrichum candidum*; *Gln*: glutamine; *Gram* $^{+ve}$: Gram positive; *Gram* $^{-ve}$: Gram negative; *GSK-3*: Glycogen synthase kinase 3; *hCE1*: human carboxylesterase1; *HGF*: hepatocyte growth factor; *HTRF*: homogeneous time-resolved fluorescence; IC_{50}: half maximal inhibitory concentration; *IL-6*:

interleukin- 6; *KATP*: ATP-sensitive potassium channel; *Ki*: drug concentration at which the reaction rate is half of Vmax; *LBD*: ligand-binding domain; LC_{50}: lethality concentration; *LPS*: lipopolysaccharide; *Lys*: lysine; *MCF7*: human tumor breast cancer cell line; *MERS*: Middle East Respiratory Syndrome; *MES*: maximal electroshock seizure; *Met*: methionine; *mGlu*: metabotropic glutamate; *MTB*: Mycobacterium tuberculosis; *NAFLD*: Non-alcoholic fatty liver disease; *PDB*: Protein Data Bank; *PDE*: phosphodiesterase; *PrP-res*: protease-resistant prion protein; *P. aeruginosa*: *Pseudomonas aeruginosa*; *PTZ*: pentylenetetrazol; *MAO*: monoamine oxidase; *SAR*: structure-activity relationship; *SARS*: severe acute respiratory syndrome; *SI*: selectivity index; *SIRTs*: Sirtuins; *SOD*: superoxide dismutase; *SRB*: sulforhodamine B; *S. pyogenes*: *Streptococcus pyogenes*; *TbrPDEB1*: trypanosoma brucei PDB1; *TGFβ*: transforming growth factor β; *TNF-α*: tumor necrosis factor α; *VEGFR-2*: vascular endothelial growth factor receptor 2.

Acknowledgements

This work was supported by the Changjiang Scholars and Innovative Research Team in Universities, Ministry of Education of China (IRT_15R55), the 9th Group of Hundred-Talent Program of Shaanxi Province (2017), the International Science & Technology Cooperation Program of Shaanxi Province (No. 2019KWZ-001), and Natural Science Foundation of Shaanxi Province, China (Grant No. 2017JM8054)

Conflict of interest

None of the authors have any conflict of interest to disclose.

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