PYRAZOLE BEARING MOLECULES AS BIOACTIVE SCAFFOLDS: A REVIEW

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ABSTRACT

Pyrazole being a heterocyclic motif has secured an eccentric status in the field of medicinal chemistry. Pyrazole and its derivatives have tremendous biological applications like anti-cancer, anti-microbial, antiviral, antifungal, anti-inflammatory, analgesic, insecticidal etc. In this review, some recent developments have been reported for the synthesis of biologically active pyrazole based molecules having biological potential such as anti-SIRT1 and SIRT2, anti-FAAH, anti-NOSs, as liver X receptor partial agonist, CB_2 receptor ligand and glucagon receptor antagonists.

Keywords: Anticancer activity, Antimicrobial activity, Anti-inflammatory/analgesic activity, Insecticidal activity, Anti-enzymatic, Pyrazole.

INTRODUCTION

Pyrazole is an important five membered aromatic heterocyclic moiety having two adjacent *N* atoms and three carbon atoms [1, 2]. Molecules carrying pyrazole moiety display a broad spectrum of pharmaceutical and biological applications such as anti-cancer, anti-inflammatory, anti-fungal, antibacterial, anti-insecticidal, analgesic, antiviral, anticonvulsant, anti-diabetic, antipyretic, anti-arrhythmic, anti-depressant, anti-hyperglycemic, anti-oxidant, herbicidal etc [3-11]. Indeed, Phenazone was the first pyrazole which was commercially available as antipyretic agent [12]. Now the fascinating medicinal potential of pyrazole could be analyzed by the lists of drugs available in market such as; Celecoxib [13], Lonazolac [14], Mepirizole [15], Rimonabant [16], acomplia [17] Cimetidine [18], Fipronil [19], Dexacoxib [20], etc.

Biological importance of pyrazole derivatives

Anticancer activity

Globally, cancer is the second major cause of increasing mortality rate after cardiovascular diseases [21] despite many treatments such as chemotherapy [22 - 23]. Pyrazole ring containing drugs have made a unique space in field of medicinal chemistry in competition of other drugs for cancer treatment such as Crizotinib and Encorafinib [24 - 27]. In order to develop novel anti-cancer drugs, Cao and coworkers in 2016 reported the synthesis of pyrazole carboxamide derivative **1** as potential anticancer agents by inhibiting MEK (IC_{50} = 91 nM in comparison to reference drug U0126 with IC_{50} = 89 nM). Compound **1** with EWD fluoro group at para position of ring B was found to be most potent pyrazole derivative also against A549 cell lines with GI_{50} = 0.26 ± 0.02 μM in comparison to reference drug Gefitinib with GI_{50} = 2.86 ± 0.18 μM (Figure 1) [28]. Reddy et al. in 2016 reported pyrazolecarboxamide derivatives **2** (Figure 1) as excellent anti-proliferative agent against MIAPaCa-2, MCF 7 and HeLa cell lines in comparison to Nocodazole as show in Table 1 [29].
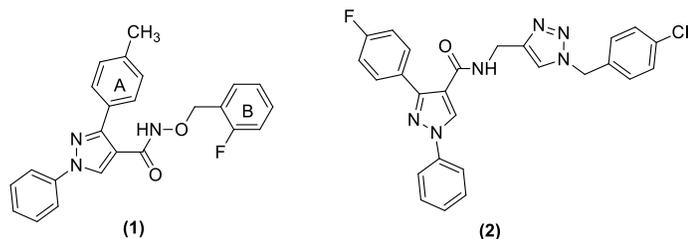

Figure 1. Structures of potent pyrazolecarboxamide derivatives **1** and **2**.

Table 1. GI_{50} (μM) values of compound **2** against various cancer cell lines

Compound	MIAPaCa-2	MCF 7	HeLa cell lines
2	0.28 ± 0.03 μM	0.13 ± 0.02 μM	0.21 ± 0.04 μM
Nocodazole (control)	0.95 ± 0.013 μM	0.94 ± 0.02 μM	0.81 ± 0.01 μM

Cinnamamide containing pyrazole derivatives were also found to be potent anti-proliferative agents as reported by Wang et al. in 2015. Improved anti-proliferative activities were observed with the following increasing order of electron withdrawing groups at para position of phenyl ring A: 4-CF_3 > NO_2 > 4-OMe > 4-F> 4-Cl > 4-Br > H > 4-Me. Moreover, the increase in activities by substitution on ring B was observed in the order as follows: 4-Me < H < 4-Br. Among all compounds, compound **3** executed well as anti-proliferative agent (with IC_{50} (μM): 0.35 μM for MCF-7, 0.62 μM for A549, 0.57 μM for B16-F10 and 1.02 μM for tubulin inhibition) (Figure 2) [30]. Vaarla et al. in 2015 reported the synthesis of coumarin based thiazolylpyrazole derivatives with moderate to good anti-proliferative activities. Compound **4** was found to be better anti-proliferative agent against HeLa cell lines with IC_{50} = 5.75 μM in comparison to reference drug Doxorubicin with IC_{50} = 3.92 μM (Figure 2) [31].
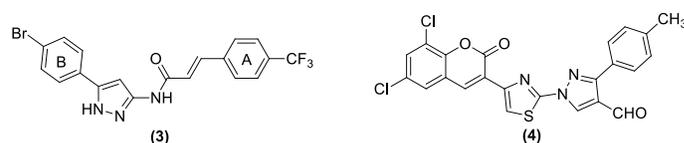

Figure 2. Structures of selected compounds **3** and **4** with potent anticancer activity.

Kamal et al. in 2015 reported the synthesis of conjugated oxindole-pyrazole derivatives as potent microtubules binders/anticancer agents. Among all, compounds **5** (Figure 3) was found to be remarkable anti-proliferative agent with average IC_{50} = 3 μM against HeLa, A549, MCF7 and DU145 cancer cell lines in comparison to the reference drug Nocodazole with average IC_{50} = 1.72 μM. It was observed that compound **5** (IC_{50} = 5.90 ± 0.78 μM) exhibited good inhibition of tubulin polymerization too. While nocodazole showed tubulin polymerization inhibition with IC_{50} = 2.2 ± 0.66 μM [32].
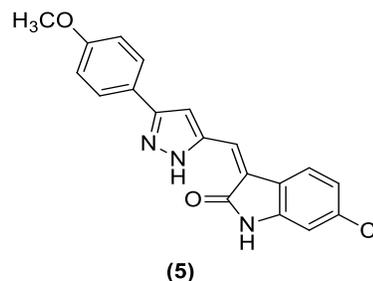

Figure 3. Oxindole-pyrazole derivative **5** as potent anticancer agent

In order to treat cancer with highly safe natural products, Zhang et al. in 2015 reported the synthesis of 23-hydroxybetulinic acid pyrazole derivatives *via* chemical modifications of triterpene derivatives. The results of MTT assay indicated the compound **6** (Figure 4) with acyl moiety in place of 23-OH group, pyrazole ring with free amine group and C-28 with electron donating bulky groups as potent in vitro anti-proliferative candidate as shown in Table 2.

Compound **6** was also suggested as best in vivo antitumor agent having 51.2 and 58.9% of inhibition against H22 liver cancer and B16 melanoma in mice as compared to parent compound HBA with 27.8 and 32.4% of inhibition, respectively [33]. Bertuzzi et al. in 2016 reported the synthesis of novel pyrazole derivatives containing lactam moiety and screened them against 5 cancer cell lines (MCF-7, MD-MB-231, HN13, V87MG and HeLa). The IC$_{50}$ values after 24 h (17.6 – 78.3 µM) and 72 h (10.6 – 33.5 µM) suggested that compound **7** (Figure 4) might be used as anti-proliferative agent [34].
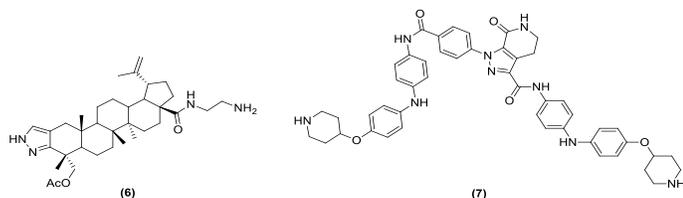

Figure 4. Structures of pyrazole derivatives **6** and **7** exhibiting good anticancer activities.

Table 2. Anti-proliferative activities (IC$_{50}$ ± SD (µM)) of compound **6**

Compound	B-16	SF-763	HL-60	BEL-7402	HeLa
6	5.58 ± 0.72	6.13 ± 0.90	8.04 ± 0.76	8.12 ± 0.41	8.97 ± 0.94
Doxorubicin	0.18 ± 0.01	0.16 ± 0.03	0.17 ± 0.01	0.22 ± 0.02	0.21 ± 0.03

Inspired by the pharmaceutical importance of fused pyrazole ring with other heterocycles Wang et al. in 2016 reported the synthesis of tetrahydropyranopyrazole derivatives containing indolyl moieties. Among all, compound **8** (Figure 5) excellently inhibited the HGC-27 and PC-3 cell lines with IC$_{50}$ = 7.70 ± 0.89 µM and 5.72 ± 0.76 µM with three times more efficacy than 5-FU (IC$_{50}$ = 25.89 ± 1.41 and 16.65 ± 1.22 µM), respectively. Moreover, compound **9** (Figure 5) inhibited the MCF-7 cell lines with moderate to good IC$_{50}$ = 3.54 ± 0.55 µM in comparison to Doxorubicin (IC$_{50}$ = 1.58 ± 0.2 µM). It was suggested that presence of –OH and –Ph groups at opposite face of pyran ring is the major cause of anti-cancer activity [35].
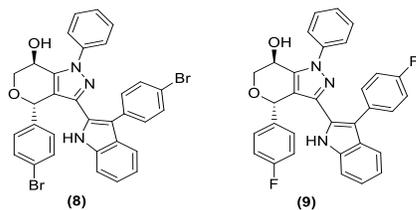

Figure 5. Structures of fused pyrazole heterocycles **8** and **9**.

The prenylation mechanism in cancer causing proteins e.g. Ras (K-Ras/N-Ras), Ral, Cdc42 and RhoC proteins etc, is catalyzed by FT and GGT1 proteins; thus medicinal chemists has been thrusted towards the development of FT and GGT1 inhibitors for the control of cancer. In order to develop novel inhibitors of prenylation enzymes, Mansha et al. in 2016 reported the synthesis of pyrazole derivatives as structural analogues of GGT1-DU40, GGT1's inhibitor. Among all, compound **10** (Figure 6) effectively inhibit the GGT1 proteins (IC$_{50}$ = 2.4 µM; with fluoro group) as compared to reference drug DU40 (IC$_{50}$ = 3.3 µM). Through MTT assay it was also observed that MDA-MB-231 cell lines were strongly inhibited by compound **10** (IC$_{50}$ = 7.6 ± 1.08 µM) in comparison to DU40 (IC$_{50}$ = 23.0 ± 1.22 µM) [36].
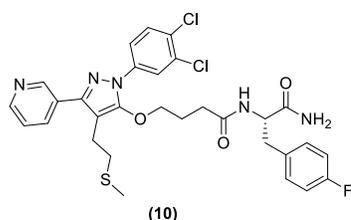

Figure 6. Structure of potent anticancer pyrazole derivative **10.**

Synthesis of pyrazolecarboxamide derivatives containing thiol moieties as surface recognition motif was reported by Wen et al. in 2016 in order to develop novel histone deacetylase inhibitors. HDAC (histone deacetylase) inhibitors assay revealed compound **11** (Figure 7) (IC$_{50}$ = 0.08 ± 0.01 µM) as highly potent inhibitor against HDACs even three folds of reference drug Vorinostat (IC$_{50}$ ± SD = 0.25 ± 0.09 µM) and its thiol based analog (IC$_{50}$ ± SD = 0.26 ± 0.06 µM). Moreover, SAR study revealed that different substituent at N-1 position promoted the inhibition activities of compounds in following decreasing order; -COOH > -OH >> -R [37]. Esvan et al. in 2016 reported the synthesis of indolopyrazole derivative containing carbazole moiety **12** (Figure 7) as more selective and potent compound against protein kinases especially Pim family (Pim 1, 2 and 3). Cytotoxicity test revealed it as moderate toxic compound with IC$_{50}$ = 4.2 and 4.5 µM against HCT116 and leukemia K562 cancer cell lines, respectively. In vitro kinase inhibition assay suggested compound **12** as good inhibitor of Pim 1and 2 (IC$_{50}$ = 0.15 ± 0.02 and 0.59 ± 0.04 µM) but excellent inhibitor of Pim-3 with IC$_{50}$ = 0.022 ± 0.009 µM but less active towards PKCα and PKC$_\gamma$ [38].
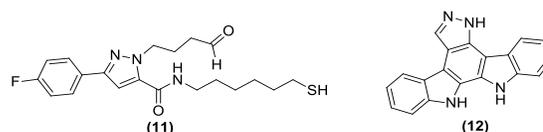

Figure 7. Pyrazole derivatives **11** and **12** with potent anticancer activities.

Carbonic anhydrase IX is an enzyme expressed in carcinomas. In order to hunt potent inhibitors of human carbonic anhydrase (isoforms IX and XII) with higher activity and more selectivity, Ibrahim et al. reported the synthesis of pyrazole derivatives as structural hybrids of benzenesulfonamide and isatin. It was observed that hCA IX (cancer associated) and XII isoforms were strongly inhibited by compound **14** with K$_i$ = 2.5 nM and compound **13** with K$_i$ = 3.7 nM (Figure 8) [39].
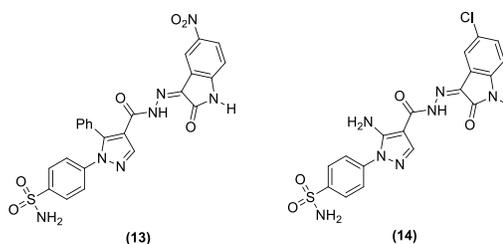

Figure 8. Structure of hCA XII and hCA IX inhibitors **13** and **14**.

Cvijetic et al. in 2015 reported the synthesis of pyrazole derivatives containing the carboxylic acid moieties exhibiting excellent inhibition against hCA IX and XII over hCAI and II with suitable inhibition constant values (k$_i$). Moreover, docking experiments were performed which also explained the selectivity and inhibition activity of these compounds against CA IX and XII. In general, the substitution pattern greatly affected the activity of the synthesized compounds; the derivatives with aryl substituents on the o- and m- position of phenyl ring were found to be active whereas, those with bulkier para-substituents were found as inactive. Fields of grid generated molecular-interaction and hydrophobic probes differentiated the active site of CA XII from other three isoforms (I, II and IX) [40].

Antimicrobial activity

Medicinal chemists have developed a variety of anti-microbial agents but the graph of resistance against many anti-microbial drugs is increasing day-by-day in many pathogens especially in different strains of bacteria [41]. There is urgent need to develop novel anti-biotics with new mode of actions, high selectivity and potency and with less time of therapy [42].

Antibacterial activity

Pyrazole being the heterocyclic motif have been utilized in order to cope the augmentation of bacterial infection and resistance against anti-biotics [43], for example, Cefoselis is a pyrazole containing anti-bacterial drug which is available in market [44], but still there is a great need to develop novel anti-bacterial drugs.

Khloya et al. in 2015 reported the synthesis and antibacterial activity of pyrazolylthiazole carboxylic acids and corresponding esters owing to the thiazole and pyrazole nuclei's specific antimicrobial activities. Among all, compound **15** (Figure 9) was found to be excellent antimicrobial agent as show in Table 3 [45]. In search of efficient antimicrobial agents, chloroquinolinepyrazole derivatives were synthesized by Miniyar et al. in 2015. Compound **16** (Figure 9) was found to be good inhibitor against gram +ve *B. subtilis* and gram –ve *E. coli* with MIC = 54 µg/ml and 43 µg/ml relative to reference drug Gatifloxacin with 30 µg/ml and 28.5 µg/ml, respectively [46].

Table 3. Antibacterial activities of compound **15** against various strains

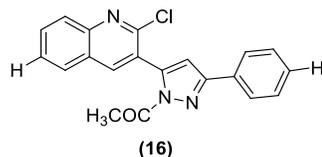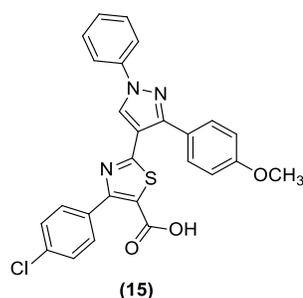| Bacterial Strain	MIC µg /mL	Zone of inhibition
Staphylococcus aureus	12.5 µg /mL	24.6 mm
Bacillus subtilis	6.25 µg /mL	29.6 mm
Ciprofloxacin	6.25 µg /mL	24 mm

Figure 9. Structures of pyrazole derivatives **15** and **16** exhibiting potent antibacterial activities.

Hussain et al. in 2015 reported the synthesis of potent pyrazole derivatives and inspected their anti-bacterial activities against *Staphylococcus aureus* (gram +ve) and *E. coli* (gram –ve). Compound **17** (Figure 10) exhibited excellent antibacterial activity with MIC = 25 µg /ml and 50 µg /ml, respectively, in comparison to Ofloxacin with MIC = 10 µg/mL and 12.5 µg /ml against *S. aureus* and *E. coli*, respectively [47]. Viveka et al. in 2015 reported the synthesis of novel pyrazoline bearing pyrazole derivatives as potent antibacterial agents.

Agar dilution method suggested compound **18** (Figure 10) (MIC = 0.2 mg/mL) as more potent candidate with 34 mm zone of inhibition than Tetracycline (MIC = 0.5 mg/mL) and Cefuroxime (MIC = 0.4 mg/mL) against *E. coli* [48].
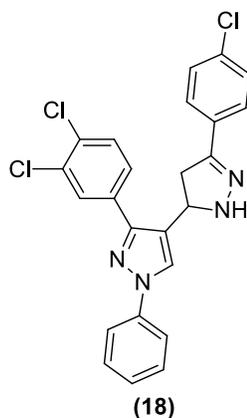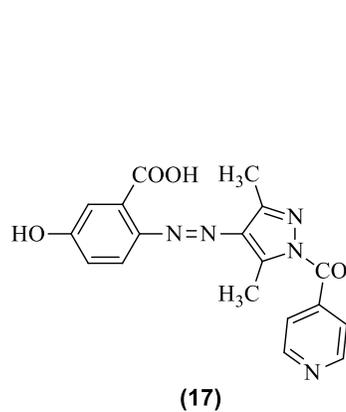

Figure 10. Structures of antibacterial candidates **17** and **18**.

In order to develop novel potential antibacterial agents, Li et al. in 2015 reported the synthesis of hybrid pyrazole derivative **19** with aminoguanidine moiety. Synthesized derivative was then evaluated for its antibacterial activities by serial dilution method and 96-well plate which revealed that compounds **19** as potent candidate (Table 4) [49].

Table 4. MIC (µg/mL) values of compound **19** against various bacterial strains
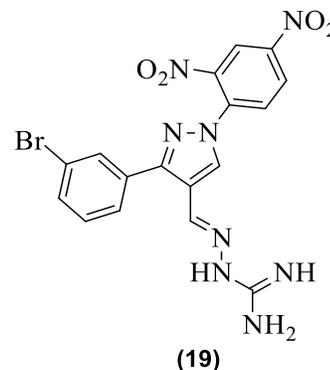
Compound	*S. aureus*	*E. coli*	MRSA 3167/3506
19	1µg/mL	2 µg/mL	1 µg/mL
Gatifloxacin	0.25 µg/mL	2 µg/mL	

Nayak et al. in 2015 reported the synthesis of pyrazole derivatives of isonicotinohydrazide as potent antibacterial agents. Microplate alamar blue assay (MABA) was performed to evaluate the antitubercular activities against *M. tuberculosis* H37Rv (MTB) which suggested that compound **21** (Figure 11) (MIC = 1.7 µM) was found to be most potent inhibitory agent whereas reference drug INH (isoniazid) exhibited MIC = 0.7 µM. Antibacterial activities were evaluated by well plate method which revealed that almost all compounds were good to moderately active against different bacterial strains. However, compound **20** (Figure 11) (zone of inhibition = 23 ± 0.2 mm against *Staphylococcus aureus*, 24 ± 0.2 mm against *Escherichia coli* and 19 ± 0.3 mm against *Pseudomonas aeruginosa*) at 75 µg/mL concentration was found to be most potent antibacterial agents as compared to reference drug Ciprofloxacin. Similar trend of antibacterial activity was observed when 50 µg/mL concentrations were used [50].
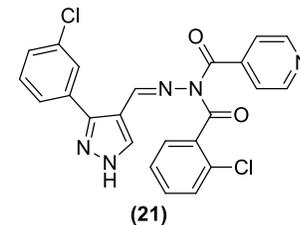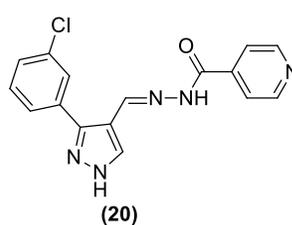

Figure 11. Pyrazole derivatives **20** and **21** exhibiting antibacterial activities.

Vaarla et al. in 2015 reported the synthesis of coumarin based thiazolylpyrazole derivatives with potent antibacterial activities. It was observed that compound **22** at 100 µg/mL concentration excellently inhibited the *P. vulgaris, E. coli* and *K. pneumonia* with 20, 22 and 24 mm zone of inhibition respectively. Compound **22** (Figure 12) was also tested for MIC (minimum inhibitory concentration) and MBC (minimum bactericidal concentration) and was found to be good inhibitor of *B. cereus, K. pneumonia* and *E. coli* with MIC = 72.8 µg/mL, 79.1 µg/mL and 86.5 µg/mL relative to reference drug Gentamycin with MIC = 10, 4 and 2 µg/mL and with MBC = 110 µg/mL, 115 µg/mL and 130 µg/mL, respectively [31].
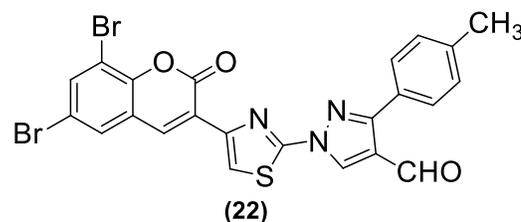

Figure 12. Antibacterial coumarin based thiazolylpyrazole derivative **22**.

Increasing mortality rate due to drug resistance bacterial strains especially MRSA (methicillin-resistant *Staphylococcus aureus*) has enormously thrusted the medicinal chemists towards the development of efficient antibacterial drugs. In order to synthesize novel NPL (natural product-like) antibacterial compounds, Yu et al. in 2015 reported the synthesis of pyrazole fused tricyclic diterpenes. Synthesized derivatives were evaluated for antibacterial activities against *S. aureus* strain Newman (Newman) and multidrug- resistant *S. aureus* strains. Among all, compound 23 (Figure 13) (MIC = 1 µg/mL) remarkably inhibited *S. aureus* Newman as compared to reference drug Totarol (MIC = 1.56 µg/mL). Against MDR bacterial strains, compound 24 (Figure 13) (MIC = 1.56 µg/mL for each) inhibited *S. aureus* NRS-1, NRS-70, NRS-100, NRS-108 and NRS-271 very efficiently [51].
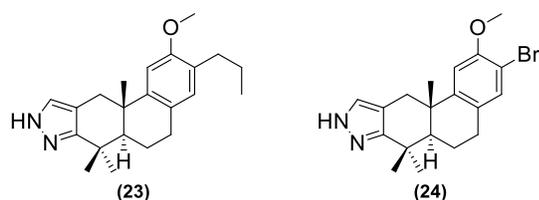

Figure 13. Antibacterial pyrazole fused tricyclic diterpenes 23 and 24.

Nayak et al. in 2016 reported the synthesis of quinoline hybrids of pyrazole derivatives in order to develop more potent compounds with better antibacterial activities. Antibacterial activities were analyzed by well plate method which revealed the zone of inhibition of compound **25** (Figure 14) (20 ± 0.3, 24 ± 0.2 and 18 ± 0.1 mm) against *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa* respectively which demonstrated its potential utility as anti-bacterial agent [52].
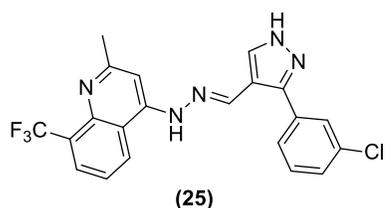

Figure 14. Structure of antibacterial quinoline hybrid of pyrazole derivative **25.**

Antifungal activity

This is usually difficult to treat fungal infection, therefore, there is need to develop more potent and highly selective anti-fungal agents such as Pyraclostrobin and Penthiopyrad [53 - 54]. In order to innovate the novel compounds with more pharmacological activities, Hussain et al. in 2015 reported the synthesis of novel diazenylpyrazole derivatives. Dish fusion method was utilized to evaluate their in vitro anti-fungal activities against fungal strain *A. niger*. It was observed that among all derivatives compound **26** (Figure 15) showed better antifungal activity (MIC = 25µg m/L) close to reference drug Ketoconazole (MIC = 12.5 µg m/L) [47]. Li et al. in 2015 reported the synthesis of hybrid pyrazole derivatives with furan-2-carbohydrazide or aminoguanidine moieties as potent pharmaceutical agents. It was observed that among all derivatives compound **27** (Figure 15) showed best antifungal activity with MIC = 1 µg/mL against *C. albicans* relative to reference drug Fluconazole (MIC = 1 µg/mL) [49].
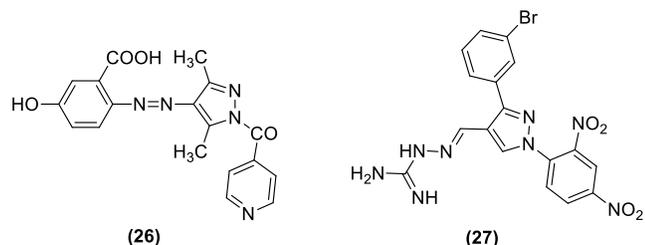

Figure 15. Structures of anti-fungal pyrazole derivatives **26** and **27.**

Sharma and co-workers in 2015 reported the synthesis of pyrazolylthiazole carboxylic acid **28** (Figure 16) and screened its anti-fungal activity against two fungal strains *Saccharomyces cerevisiae* and *Candida albicans*. It was observed that compound **28** (Figure 15) with 27.6 mm (MIC 6.25 µg/mL) zone of inhibition showed better results against both strains in comparison to reference drug Amphotericin B with zone of inhibition 19.3 mm (MIC = 6.25 µg/mL) and 16.6 mm (MIC = 6.25 µg/mL), respectively [45]. In search of efficient antifungal agents, chloroquinolinepyrazole derivatives were synthesized by Miniyar and coworkers in 2015. It was observed that antifungal activity was greatly dependant on substitution pattern and increased by introducing electron donating groups at para position as compared to electron withdrawing groups. Compound **29** (Fig. 16) (p-amino derivative) was found to be more promising antifungal agent with MIC = 46 µg/ml against *P. notatum* and MIC = 48 µg/ml against *A. fumigatus* relative to reference drug with MIC = 30.5 & 32.5 µg/ml, respectively [46].
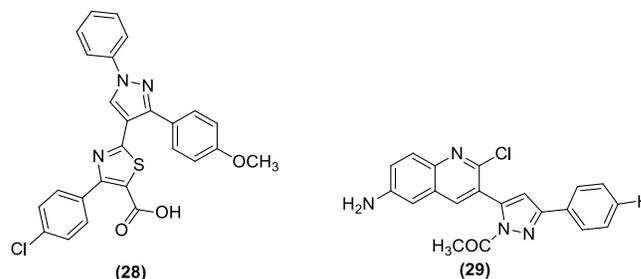

Figure 16. Structures of pyrazole derivatives **28** and **29** with antifungal activities.

Antiviral

Pyrazole derivative **30** (Figure 17) was synthesized by Jia et al. in 2016 and was reported as potent inhibitor against secretion of HBsAG (surface antigen of HBV) (IC_{50} = 24.33) and HBeAG (envelop antigen of HBV) (IC_{50} = 2.22) [55]. In order to hunt potent anti-BVDV (bovine viral diarrhea virus) agents as well as molecules with efficient DNA binding/cleaving activities, Han et al. in 2015 reported the synthesis of alternate novel pyrazole derivatives bearing tetramic acid subunits. Electronic absorption study of the synthetic derivatives suggested that metal complexes (Cu (II)) of compound **31** having no *N*-substituent on pyrazole ring were found to be good DNA binder. Ligand dependant DNA cleavage studies were performed which revealed that at pH 7 complex 3b -Cu^{2+} (0.20 mmol/L conc) with 24 h incubation at 37 ºC showed the remarkable supercoiled DNA (pUC 19 plasmid DNA) cleavage to nicked DNA *via* hydrolytic pathway. Anti-BVDV activities of selected compounds were inspected on MDBK cells *via* MTT assay. It was observed that compound **32** (Figure 17) (EC_{50} = 0.12 µmol/L) performed well as anti-viral agent as compared to reference drug Ribavirin (EC_{50}= 1.3 µmol/L) [56].
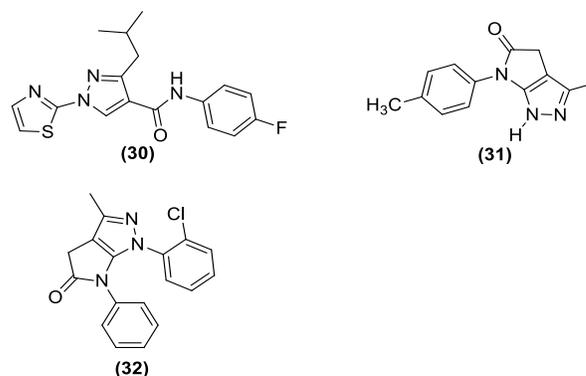

Figure 17. Structures of selected compounds **31** and **32** against BVDV.

Anti-inflammatory and analgesic effects

Long term use of non-steroidal anti-inflammatory drugs becomes the cause of gastric ulceration and bleeding [57]. Synthesis of NSAIDs (non-steroidal anti-inflammatory drugs) with less damaging upshots has seizured the heed of pharmacists.

Hussain et al. in 2015 reported the synthesis of novel diazenylpyrazole derivatives and scrutinized their anti-inflammatory activity by carrageenan-induced rat paw edema method which disclosed compound **33** (Figure 18) as best anti-inflammatory agents (with 80.29% anti-inflammatory activity very close to reference drug ibuprofen (80.38%). It was observed that compounds having less gastro-intestinal ulceration activity also showed less lipid peroxidation in the range of 3.25 ± 0.05, on the other hand reference drugs flurbiprofen (7.51 ± 0.68) and ibuprofen (7.79 ± 0.13) showed higher index of lipid peroxidation, additionally did not exhibited histopathology of liver. As well as compound **33** was also manifested as moderate pain killer with less ulcerogenic effects with activities running between 0.333 ± 0.10 to 1.000 ± 0.31 while 2.000 ± 0.13 and 1.666 ± 0.24 were the ulcerogenic activities of Flurbiprofen and Ibuprofen [47].
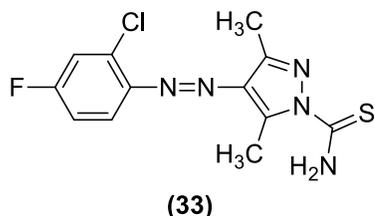

Figure 18. Structure of pyrazole based anti-inflammatory compound **33**.

Pyrazolylthiazole carboxylic ester **34** was prepared by Khloya et al in 2015. Carrageenan-induced rat paw edema method revealed that compound **34** (Figure 19)(93.06%) exhibited excellent anti-inflammatory activity after 3 h of carrageenan injection in comparison to reference drug Indomethacin (91.32% AI) [45]. Viveka et al. in 2015 reported the synthesis of novel pyrazoline bearing pyrazole derivatives as potent anti-inflammatory agents. Carrageenan-induced rat paw edema method suggested compound **35** containing *N*-acyl moiety with 75.56% inhibition within 120 min of reaction time, as potent anti-inflammatory compound (Figure 19). Analgesic activities were tested by tail flick latency test and compound **35** (Figure 19) with 7.7 ± 0.1 tail flick latency in secs was found to be exhibited best analgesic effects very close to Pentazocin (with 7.7 ± 0.1 tail flick latency in secs) [48].
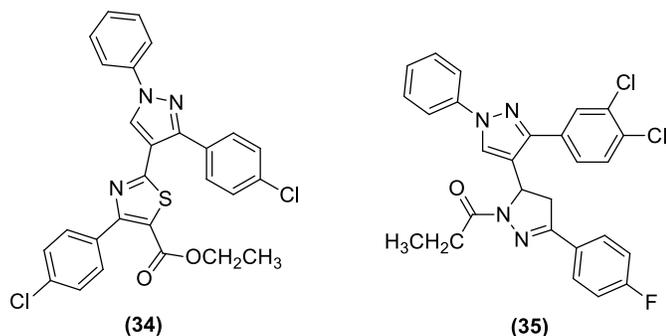

Figure 19. Structures of anti-inflammatory and analgesic agents **34** and **35**.

In order to synthesize safe NSAIDs, Abdellatif et al. in 2015 reported the synthesis of pyrazoline and pyrazole derivatives as celecoxib analogs. The synthesized pyrazole and pyrazoline were further evaluated for biological activities as anti-inflammatory agent and cyclooxygenase 1 and 2 (COX-1 and COX-2) inhibitors. In vitro cyclooxygenase inhibition assay which was carried out to evaluate inhibition activities of targeted compounds which revealed that synthesized derivatives were excellent inhibitors of COX-2 ($IC_{50} = 0.97$-10.8 µM) but poor inhibitors of COX-1 ($IC_{50} = 5.6$-24.1 µM). Moreover, compounds **36** (Figure 20) ($ED_{50} = 190.5$ µmol/Kg) with 41.3% inhibition was found to be most potent AI candidate more than the reference drugs Aspirin ($ED_{50} = 710$ µmol/Kg po) and Ibuprofen ($ED_{50} = 327$µmol/Kg po) but less effective than Celecoxib ($ED_{50} = 30.9$ µmol/Kg po) [58]. In order to develop novel potential AI's (anti-inflammatory) agents, Li et al. in 2015 reported the synthesis of hybrid pyrazole derivatives with furan-2-carbohydrazide or aminoguanidine moieties. Ear edema method (induced by xylene) was used for the evaluation of anti-inflammatory activities of synthesized derivatives. Excellent inhibition rate (93.59%) was shown by compound **37** (Figure 20) greater than the reference drugs Indometacin (45.23 %) and Ibuprofen (29.56%) [49].
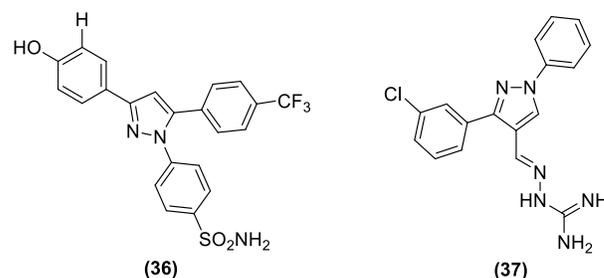

Figure 20. Structures of compound **36** and **37** potent anti-inflammatory activity.

Based upon the concept of bioisosterism, EI-Feky et al. in 2015 reported the synthesis of novel pyrazole derivative **38** bearing quinolines *via* Pfitzinger reaction II. Their COX (cyclooxegenase) inhibition activity was checked by using COX-1/COX-2 assay kit which revealed compound **38** (Figure 21) having electronegative atom chlorine as potent inhibitor of COX-2 with $IC_{50} = 0.26$ µM and SI > 192.33 in comparison to Celecoxib ($IC_{50} = 0.28$ µM with SI > 178.57). In case of COX-1 all derivatives as well as Celecoxib showed $IC_{50} > 50$ µM. Moreover, compound **38** with 0.75 ± 0.03 mm thickness of paw skin was found to be good anti-inflammatory agent whereas the reference drug Celecoxib showed 0.7 ± 0.02 mm thickness of paw skin [59]. Thore et al. in 2016 reported the synthesis of methylthiopyrazole derivatives containing carboxylate moieties. Carrageenan induced paw edema method revealed the potent anti-inflammatory activity of **39** (Figure 21) with 44.48% inhibition while diclofenac exhibited 46.20% of inhibition after 2 h of treatment. Compound **39** was also tested for ulcerogenic effect. It was found that tested compound showed less ulcer index with 1.12 ± 0.62 ulcer indexes in comparison to standard drug with 3.10 ± 0.75 ulcer indexes [60].
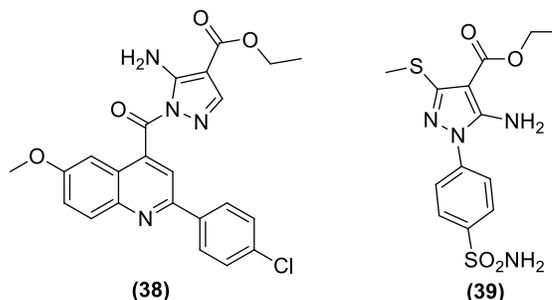

Figure 21. Structures of pyrazole based anti-inflammatory compounds **38** and **39**.

Insecticidal activity

Now-a-days among the most serious threats in crop health and protection are the agrochemical pests and insects [61]. Pyrazole being a heterocyclic moiety have played a major role in agro chemistry. Cyantraniliprole, Chlorantraniliprole and Pyriprole are one of those pyrazolederivates that are available in market as commercial pesticides [62]. Involvement of EcR-USP (ecdysone receptor-ultraspiracle protein) heterodimeric receptors in molting has coaxed the pharmacists towards the synthesis of potent EcR-USP based ligands to assist and enhance the ecdysis in environmental friendly insects. In this context, Deng et al. in 2016 reported the synthesis potent ligands of heterodimeric EcR-USP as structural analogues of BYIO6830 and VS008 having potent insecticidal activity against few lepidopteran pests too. The synthesized pyrazole amide derivatives were then evaluated for their insecticidal activities against *Helicoverpaarmigera, Mythimnaseparata* and *Pyraustanubilalis*. It was observed that among all, compound **40** with 3-methoxy group exhibited potent activities in comparison to positive control of Tebufenozide. Compound **40** (Figure 22) was found to be most potent compound with 100% mortality rate against all insects. Moreover, molecular docking studies were performed to investigate the target site on EcR subunits, binding free energy of ligands and to investigate the ligand's binding mechanism at active site of EcR subunits and it was observed that mode of action of compound **40** was similar to Tebufenozide as EcR-USP heterodimeric binder [63].
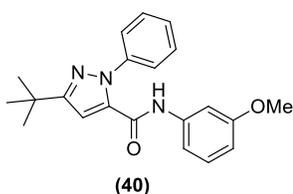
(40)

Figure 22. Structure of heterodimeric EcR-USP pyrazole derivative **40**.

In order to get best insecticidal compounds, chiral 1-(3-chloropyridine-2-yl)-3-) trifluoromethyl)-1*H*-pyrazole-4-carboxamide derivatives were synthesized by Liu et al. in 2016 *via* successful incorporation of flexible alkyl chain between benzene ring and trifluoromethylpyridine. The synthesized fluorinated pyrazolecarboxamide derivatives were further evaluated for their inhibition activities (100% at 40 m) against the tomato root-knot nematode disease caused by *Meloidogyne incognita.* The docking study revealed that among other derivatives compound **41** (Figure 23) was found to be more potent and exhibited best binding mode with AchE (acetyl cholinesterase) *via* two *H* bonds [64].
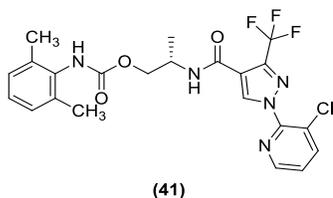

(41)

Figure 23. Structure of pyrazole derivative **41** exhibiting insecticidal activity.

Immunosuppressant activity

Pyrazole derivatives containing *O*-benzyl oxime moiety were synthesized as more potent immunosuppressive agents with less toxicity by Lv et al. in 2016. Structural modifications suggested that immunosuppressive activity increased by varying para substituent on ring A and ortho substituent on ring B with electron withdrawing groups in following order respectively; F > Cl > OMe > H > Me (for ring A) and F > Cl > H (for ring B). P13KƔ enzymatic inhibitory activity of selected compounds was also checked which also suggested compound **42** (IC$_{50}$ = 7.2 µM) was the best potent candidate as compared to reference compound LY294002 (IC$_{50}$ = 7.2 µM). Cytotoxicity and inhibitory activities were evaluated of pyrazole derivatives on lymph node cells and by inhibiting proliferation of T. cells stimulated by ConA (concanavalin A) respectively, which suggested that compound **42** (Figure 24) was most potent with less toxicity (CC$_{50}$ ± SD = 259.12 ± 22.72 µM) and excellent inhibitory activity (IC$_{50}$ ± SD = 1.18 ± 0.26 µM). Moreover, compound **42** was also found to be most potent compound which showed strong inhibition against the expression of IL-6 mRNA [65].
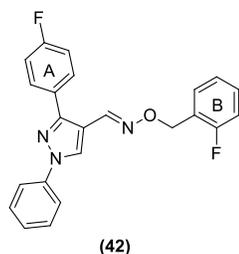

(42)

Figure 24. Immunosuppressive agent **42** based on pyrazole ring.

Anti-enzymatic

Anti-SIRT1 and SIRT2

While working on the development of new unparalleled compounds with inhibitory activity against sertuin enzymes class III SIRT1 and SIRT2, Therrien et al. in 2015 reported the synthesis of bicyclic pyrazole derivatives. In general, the synthesized hydrate bicyclic pyrazole derivatives showed moderate to low inhibitory activities. Among all derivatives, compound **43** (Figure 25) was found to be most active, however, with moderate inhibitory activity against SIRT1 with IC$_{50}$ = 1 µM and with low inhibitory activity against SIRT2 (IC$_{50}$ = 43%) [66].
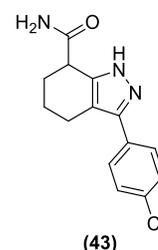
(43)

Figure 25. Structure of pyrazole based anti- SIRT1 and SIRT2 compound **43**.

Anti-FAAH

The degradation of neurotransmitters by FAAH (fatty acid amide hydrolase) resulting in neuropathic pain has posed a challenge for scientists. In order to come across potent compounds with desired inhibitory activities, Tabrizi and coworkers in 2015 synthesized a series of pyrazole derivatives containing phenyl cyclohexyl carbamate moiety. Among selected active compounds, compound **44** (Figure 26) was found to be most vigorous inhibitor against FAAH with IC$_{50}$ = 11 nM even greater than the reference drug CAY10499 (IC$_{50}$ = 14 nM) [67].
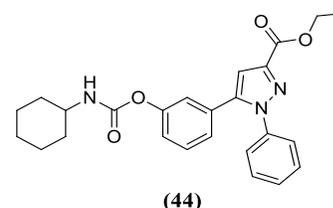

(44)

Figure 26. Structure of selected compound **44** against FAAH.

Anti-nitric oxide synthase (NOSs)

Nieto et al. in 2015 reported the synthesis of trifluoromethylpyrazole derivatives based upon hemicurcuminoids. Synthesized compounds were then evaluated for their inhibition potential against NOSs (nNOS, iNOS and eNOS). Among all, compound **45** (Figure 27) strongly inhibited the eNOS with almost 56.8% inhibition. While compound **46** efficiently inhibited the nNOS and iNOS with almost 52.9% and 68.8% inhibition (Figure 27) [68].

(45)   **(46)**
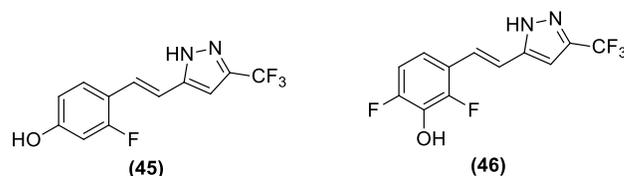
Figure 27. Pyrazole based anti-nitric oxide synthase **45** and **46**.

Liver X Receptor (LXR) partial agonist

For the synthesis of liver X receptors especially LXRβ agonist's Kick and coworkers in 2015 reported the synthesis of imidazole and pyrazole derivatives. Pyrazole and imidazole derivatives then evaluated for biological activities especially for LXRα agonism and LXRβ selectivity. Best results were obtained in case of compound **47** (Figure 28) which was found to be LXR partial agonist showing 72% LXRβ selectivity [69].

(47)

Figure 28. Structure of LXR partial agonist **47**.

CB₂ receptor ligands

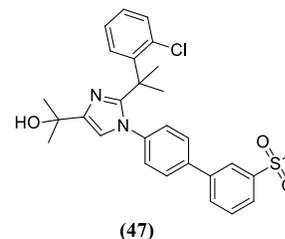CB₂ receptors being the part of neurons and brain cells have been identified responsible to control the movement, sensory perception, memory and emotions etc. Thus, it becomes meaningful for medicinal chemists to target CB₂ receptors for the treatment of neurological disorders. In this regard, Deiana et al. in 2016 reported the synthesis of tricyclic pyrazole derivatives with variety of carboxamides as antagonist agonist of CB₂ receptor. According to Radio ligand assay compound **48** was found to be more potent with better affinities towards CB₂ receptors with K_i values (6 ± 1 nM). Whereas, reference compounds A and B showed 0.037 ± 0.003 nM and 1079 ± 44 nM K_i values respectively. Moreover, Compound **48** (Figure 29) was found to possess remarkable selectivity towards CB₂ receptors with K_iCB_2 selectivity > 6944. Functional activities at CB₂ receptors were also evaluated of synthesized compounds *via* GTP$_\gamma$S assay and found to be antagonist agonists. Compound **48** was found to be most potent candidate with $IC_{50} = 80.4 \pm 17.0$ nM [70].
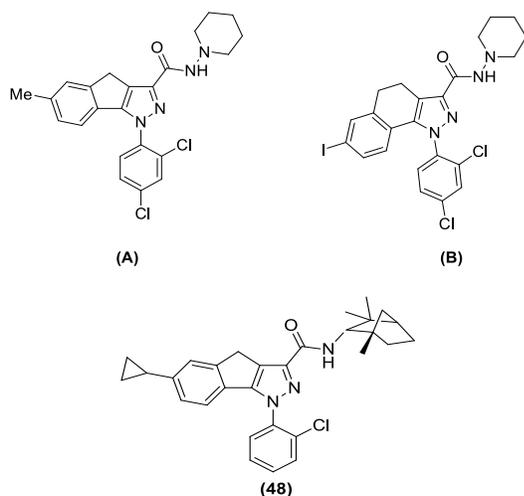

Figure 29. Structure of CB₂ receptor ligand **48**.

Glucagon receptor antagonists

Day-by-day increasing rate of insulin resistance and hyperglycemia due to type 2 diabetes mellitus (T2DM) has mediated the scientists towards the synthesis of more efficient and safer drugs. In this regard, Shu et al. in 2016 reported the synthesis of novel pyrazole derivative as antagonists of glucagon receptors based on conformational restrain and bioisoteric strategies. *In vitro* glucagon receptors antagonism activity and functional cAMP activities of the synthesized compounds revealed compound **49** (Figure 30) to be potent GCGR binder ($IC_{50} = 3.6 \pm 0.5$ μM) with good cAMP response (1.2 ± 0.3 μM) [71].
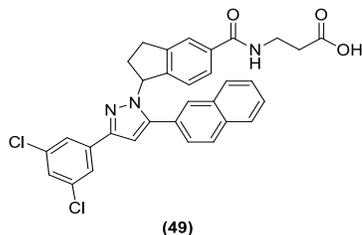

Figure 30. Pyrazole based glucagon receptor agonist **49**.

CONCLUSIONS

From the above literature survey, we could conclude that pyrazole has immensely turned the interest of medicinal chemists towards the synthesis of its biologically active derivatives. These pyrazole derivatives have fascinating display of pharmacological profile. This comprehensive review will provide the bioactivities of medicinally important pyrazole derivatives against divergent diseases. Also, with the alarming situation of health problems, the quest to develop more potent and highly selective pyrazole derivatives should be continued.

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