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Review Article

RECENT REPORTS ON PYRAZOLE-BASED BIOACTIVE COMPOUNDS AS CANDIDATE FOR ANTICANCER AGENTS

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ABSTRACT

Pyrazole is a five-membered heterocyclic compound containing two nitrogen atoms. Due to its biological significance, design of novel pyrazole derivatives has become an interesting research area. We report the current progress in the development of anticancer agents containing pyrazole ring covering the time span of the past few years (2013–2016). The presence of this nucleus is accompanied with some side chains, functional groups, or in combination with other nucleus such as thiazole, thiourea, glucosamine, naphthalimide, and benzofuran. Several biologically active pyrazoles synthesized by numerous researchers across the world are summarized in this paper.

Keywords: N-heterocyclic, Pyrazole, Synthetic derivatives, Anticancer agents.

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INTRODUCTION

N-containing heterocycles are molecules which have unique structural motif and found extensively in natural products such as hormones, alkaloids, and vitamins [1,2]. Pyrazole represents one of the most prominent classes of heterocycles exhibiting large spectrum of biological performances such as anticancer [3,4], antitumor [5], anti-AIDS [6], antimicrobial [7,8], antimalarial [9], and antitubercular [10]. It gained great attention since the privileged structure is commonly found as active constituent in commercial drugs (Fig. 1), such as lonazolac 1 nonsteroidal anti-inflammatory drug (NSAID), pyrazofurin 2 (anticancer), difenamizole 3 (analgesic), and deracoxib 4 (NSAID) [11-14]. The simplicity of preparation and rich of biological benefits of pyrazole and its derivatives make them as interesting platform chemicals for organic, medicinal, and pharmaceutical chemistry.

Chemically, in the basic structure, pyrazole has two nitrogen atoms at adjacent position in the five-membered ring [15]. Molecular formula of pyrazole is $C_3H_4N_2$ which has 6 π electrons delocalized in ring forms an aromatic system. Pyrazole is closely linked with several of its reduced or oxidized form such as pyrazoline, pyrazolidine, and pyrazolone (Fig. 2). Unlike pyrazole, pyrazoline, and pyrazolidine are not aromatic compounds due to lack of conjugation and delocalization of π electrons. The main skeletal of pyrazole and its related structures can be utilized as important building blocks in organic synthetic for the design of a variety of biologically active compounds [16,17]. In this review, we collect research result about the potency of pyrazole derivatives as anticancer agents.

DISCUSSION

With the shift in the people's living habit, cancer has become a deadly disease in both developed and developing countries across the globe [18]. It is caused by miss-regulation or mutation of the cell cycle that regulate genes and proteins. Cancer is a group of various diseases, i.e., lung cancer, cervical cancer, prostate cancer, and breast cancer, and all of them are characterized by an abnormal control of cell growth [19]. Despite many clinically successful anticancer drugs have been developed either natural products or synthetic derivatives of naturally occurring lead compounds, there are still limitations in the treatment of cancer including the effectiveness of drugs and serious side effects [20]. Hence, many pyrazole-based compounds have been synthesized and screened by scientists.

Discovery of some pyrazoles in the year 2013

Molecular structures of pyrazole derivatives prepared by several research group during 2013 were presented in Fig. 3. Some new compounds of pyrazole-based 1,3-thiazoles and 1,3,4-thiadiazoles were synthesized by Dawood *et al*. and evaluated for anticancer activity against HepG2, MCF-7, and A549 cell lines [21]. Following *in vitro* evaluation, it was reported that there are 9 compounds (9a-c, 10a-b, 11, and 12a-c) that have IC_{50} values below 100 μM. Compound 9a showed anticancer potency with IC_{50} value of 67.11 μM against HepG2 cell line but inactive against MCF-7 and A549 cell lines. Introduction of electron donating group (4-Me and 4-OMe) to compounds 9b and 9c enhanced their anticancer activity with IC_{50} range of 20.74-64.50 μM against the aforementioned cancer cell lines. Compounds 10a and 10b (IC_{50} values between 8-16 μM) were reported as the most active compounds of the series against three model cancer cell lines. They have greater activity compared to compounds 11 and 12a-c [21]. A new series of pyrazole-based acyl thiourea derivatives synthesized by Koca *et al.* was screened for their anticancer potential against DLD-1, HepG2, and Jurkat cell lines [22]. Compounds 13a-k have shown good anticancer activity which has % cell viability after 48 h in the range of 6.00-90.00 (against Jurkat cell line), 40.25-96.56 (against DLD-1 cell line), and 20.81-51.24 (against HepG2 cell line). Compound 13a is the most potent pyrazole in this series which has 6.00 ± 0.61% cell viability against Jurkat cell line at sample concentration of 10^{-4} M [22].

El-Gamal *et al*. developed novel structures bearing triarylpyrazole scaffold and determined their anticancer performance [23]. Surprisingly, all tested compounds (14a-m) demonstrated superior anticancer activity against over 60 cancer cell lines including RPMI-8226, HOP-92, KM12, SF-295, MDA-MB-435, OVCAR-3, A498, PC-3, and MDA-MB-468. Triarylpyrazole 14h was reported as the most active anticancer agent with IC_{50} ≤0.63 μM [23]. Another series of pyrazole derivatives in the form of 2-oxo-2*H*-chromenylpyrazolecarboxylates 15a-c and 16a-d with a potent performance against prostate (DU-145), lung adenocarcinoma (A549), and cervical (HeLa) cancer cell lines was described by Kumar *et al*. [24]. These compounds displayed appreciable anticancer potency against all the tested cell lines with IC_{50} values between 24 and 40 μM (on DU-149), 18-52 μM (on A549), and 22-50 μM (on HeLa).

Thirty derivatives of pyrazole and pyrazoline bearing isosteviol moiety (17a-17ad) were synthesized by Zhu *et al*. [25]. The cytotoxic activities were evaluated *in vitro* against four human cancer cell

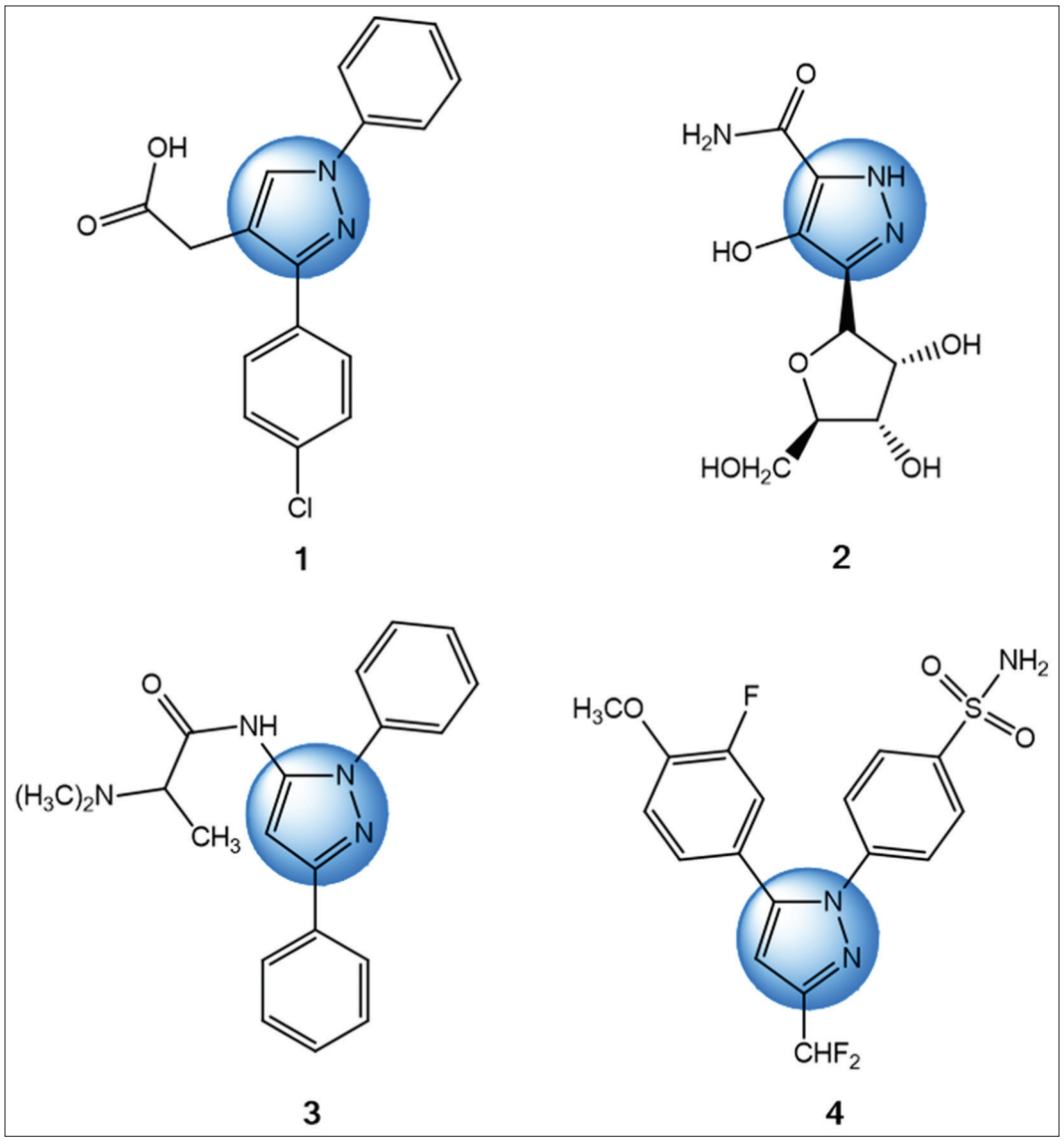

Fig. 1: Several commercial drugs containing pyrazole ring

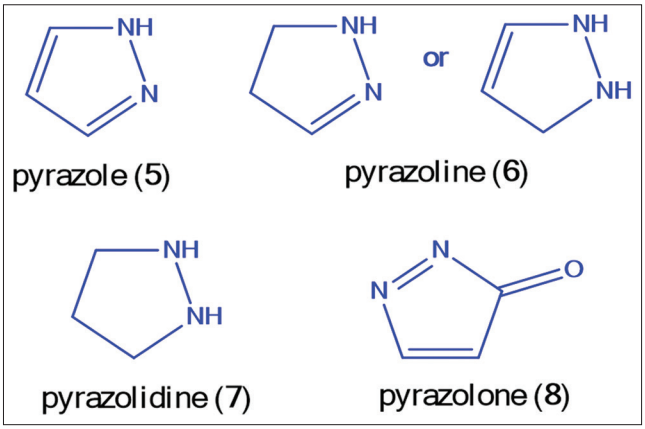

Fig. 2: Basic structure of pyrazole and related compounds

lines. Out of the synthesized compounds, compound 17t was found to be the most potent anticancer candidate with IC_{50} values of 1.09, 2.71, 3.18, and 13.52 μM against Raji, SGC7901, A549, and HeLa, respectively [25].

Discovery of some pyrazoles in the year 2014

Fig. 4 showed new pyrazoles synthesized in 2014. Grosse *et al.* presented a paper on imidazo[1,2-b]pyrazoles that are useful as inhibitors of 5 human and 1 murine cancer cell lines [26]. Of the 39 compounds screened *in vitro* by MTT assay, compound 18a, 18b, 19, and 20 displayed an IC_{50} below 10 μM. The structure-activity relationship analysis resulted preliminary conclusion that C-7 aminomethylated compounds containing 6-membered cycle like *N*-methylpiperazine or morpholine have high anticancer potency. On the contrary, in C-2/C-3/C-6/C-7 tetrasubstituted imidazo[1,2-b]pyrazoles, the presence of a fourth substituent has not influence to enhance the anticancer activity, except in the case of compound 20 [26].

The synthesis and inhibitory activity against A549 lung cancer cell line of a series of 2-(3,5-dimethyl-1H-pyrazol-1-yl)-1-arylethanones were described by Kumar *et al.* [27]. *In vitro* anticancer test was performed against colon (HCT-116 and HT-29), lung (A549), prostate (DU-145), and ovarian (SKOV3) cell lines. Compound 21a was found to be cytotoxic to all cancer cell lines, except SKOV3. Furthermore, compound 21a and 21b exhibited similar activity as carboplatin in inhibiting viability of A549 cancer cell line [27]. Li *et al.* reported the synthesis of 4-pyrazolyl-1,8-naphthalimide derivatives (22a-l) [28]. All compounds were toxic against MCF-7 and HeLa that have IC_{50} values of 0.51-17.01 μM (on

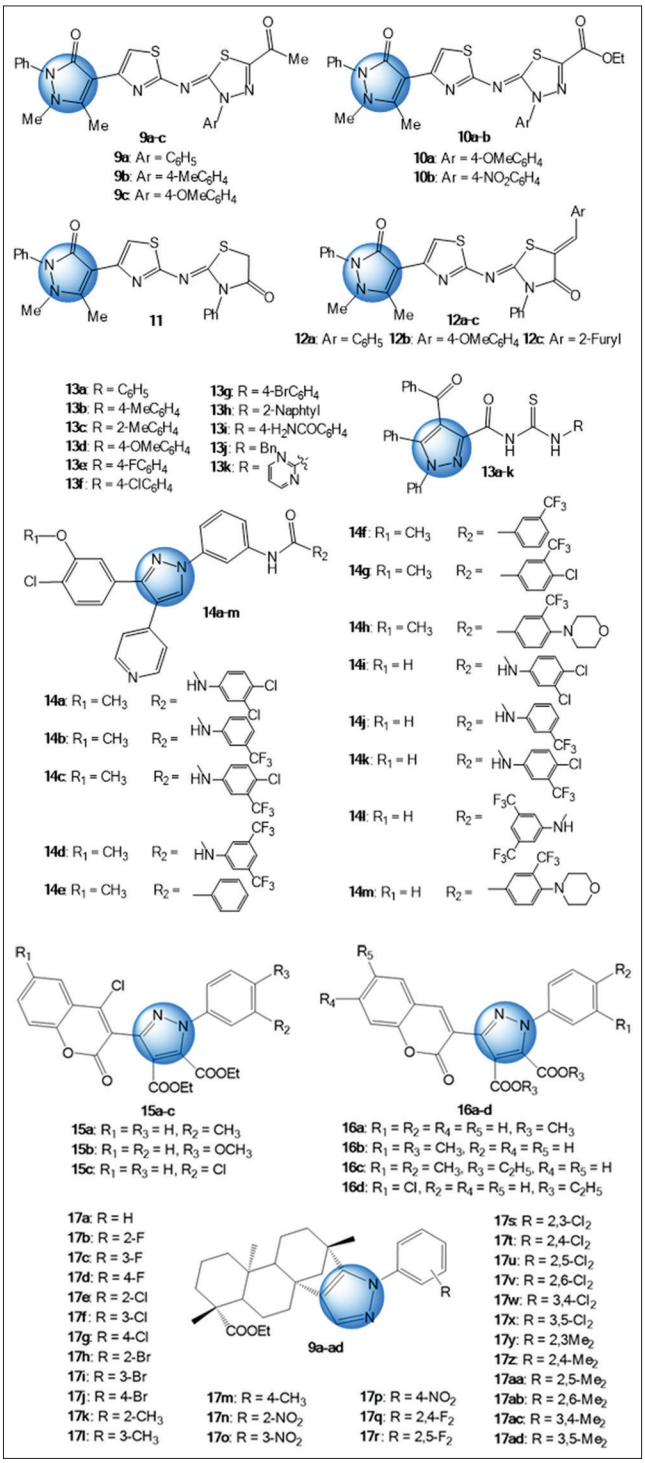

Fig. 3: Pyrazole derivatives discovered during the year 2013

MCF-7) and 3.09-16.60 μM (on HeLa). Toward these cells, compound 22b, 22h, and 22i have higher cytotoxicity than amonafide (control). On A549 cell, most of the synthesized compounds have good anticancer activity (IC_{50} values between 5.09 and 25.36 μM), except compound 22d and 22l, displayed IC_{50} values more than 50 μM [28].

The compounds of 5-(p-tolyl)-1-(quinoline-2-yl)pyrazole-3-carboxylic acid amides with potent antiproliferative activity against human liver, breast, and colon carcinoma cancer cell lines were developed by Pirol *et al.* [29]. In the series that contain 15 synthesized bioactive molecules, compound 23 with 2-chloro-4-pyridinyl group in the amide part showed promising cytotoxic performance against all the above-mentioned cancer cell lines with IC_{50} values of 1.6 μM (on liver cancer cell), 3.3 μM (on breast cancer cell), and 1.1 μM (on colon carcinoma cancer cell). It induced apoptosis with significant cell cycle arrest at SubG1/G1 phase in human liver cancer cell line.

A series of derivative compounds which contain pyrazole-thiazole-naphthalene hybrid was synthesized by Yuan *et al*. [30]. Of the 28 compounds evaluated, 30d exhibited the most potent inhibitory activity against HeLa with IC_{50} of 0.86 μM. SAR analysis revealed that the presence of electron donating group enhanced the antiproliferative activity (-OMe > -Me > -H > -Br > -Cl > -F). Moreover, compound with 4-thiazolinone moiety displayed higher inhibitory activity than compound bearing a 4-phenylthiazolinone group.

Discovery of some pyrazoles in the year 2015

El-Karim *et al*. discovered a novel series of benzofuran-pyrazole derivatives as anticancer agents [31]. Resultantly, compound 31a exhibited a notable anticancer activity against Leukemia CCRF-CEM, MOLT-4, ovarian cancer IGROV1, CNS cancer SNB-75, melanoma SK-MEL-2, colon cancer HCC-2998, renal cancer 786-0, RXF 393, lung cancer HOP-92, breast cancer HS 578T, and T-47D lines with IC_{50} values between 1.00 and 2.71 μM. Molecular docking study revealed that compound 31a has fulfilled Lipinskiís rule of five. Furthermore, good anticancer activity of compound 31a, 31b, and 32 could be attributed to the presence of benzofuran-N-phenylpyrazole skeleton together with the 3-pyrrolo/furano-N-acetyl pyrazoline or 3-pyrrolo-isoxazole ring systems. Kamal *et al*. developed a series of pyrazole-oxindole conjugates through Knoevenagel condensation [32]. Compound 33a-c was proved to be the three best molecules in inhibiting the cell growth of HeLa, A549, MCF-7, and DU-145 with IC_{50} values in the range of 2.4–9.3 μM. The presence of a single chloro or methoxy group at D ring was found to be important for the antiproliferative and antitubulin polymerization activity. Notably, from Zebrafish screening assays showed that compound 33a and 33c caused developmental defect of embryos (Fig. 5).

Among the 1,3-diphenyl-1H-pyrazoles that contain benzimidazole moiety developed by Reddy *et al*., most of the synthesized compounds significantly inhibit the proliferation of cancer cell and some of them have excellent antiproliferative action than 5-fluorouracil as control [33]. Compound 34a-c demonstrated potent large spectrum cytotoxicity against A549, HeLa, and MCF-7 cancer cell lines with IC_{50} values in the range of 0.83–1.81 μM. Compound 35 which has 5-fluoro-pyridin and 4-fluoro-phenyl moiety showed the highest inhibition in human MCF-7 and HeLa cell lines among the new series of biomolecules synthesized by Sankappa *et al*. [34]. A new series of steroidal oxadiazole, pyrrole, and pyrazole derivatives was developed by Shamsuzzaman *et al*. resulted in compound 36 as the most promising anticancer candidate [4]. This study also reported that pyrazole moiety after being attached with steroidal skeleton may be the factor responsible for enhanced anticancer properties of pyrazoles. Various novel pyrazole-5-carboxamide and pyrazole-pyrimidine derivatives were synthesized by Shi *et al.* and were tested for antiproliferative activity against MGC-803, SGC-7901, and Bcap-37 cell lines *in vitro* [35]. Compound 37 was recorded to be a promising anticancer agent. Several coumarin substituted thiazolyl-3-aryl-pyrazole-4-carbaldehydes were designed by Vaarla *et al*. [36]. Compound 38a and 38b showed an appreciated inhibition against MCF-7, HeLa, and DU-145 cell lines.

Discovery of some pyrazoles in the year 2016

Two series of substituted phenyl pyrazoles were developed by Alam *et al.* and were tested as inhibitor for several cancer cell lines [3]. As a result, compound 39 displayed superior cytotoxicity with an IC_{50} value of 14.31 ± 0.90 μM for MCF-7, 8.55 ± 0.35 μM for NCI-H460, and 7.01 ± 0.60 μM for HeLa. This compound showed *in silico*

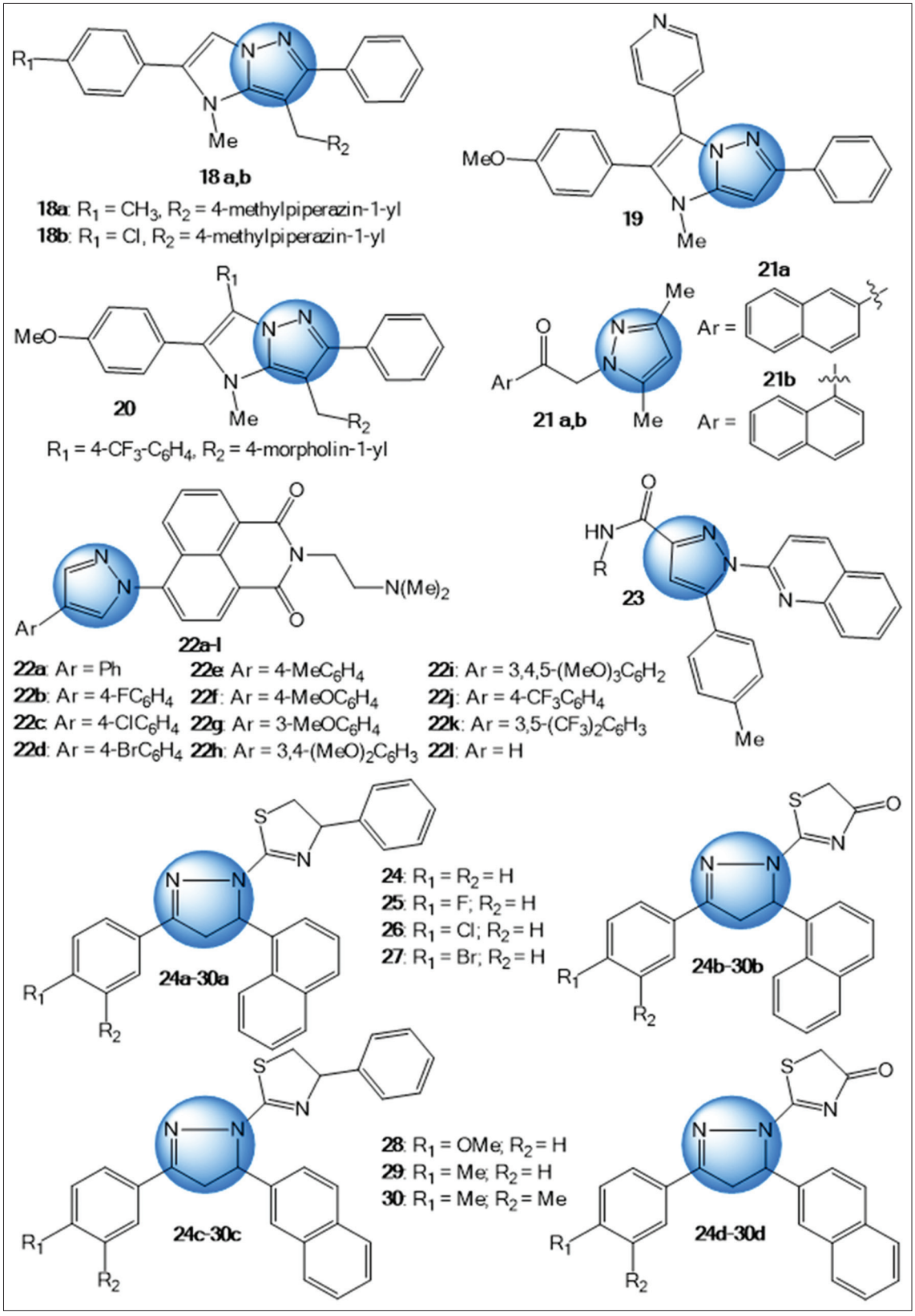

Fig. 4: Pyrazole derivatives discovered during the year 2014

drug-likeliness properties within the acceptable range. Dai *et al.* synthesized a series of novel pyrazole oxime derivatives containing a 1,2,3-thiadiazole scaffold [37]. Compounds 40a, 40c-e were the most active against HCT-116 cells with IC_{50} values below 8.50 μM. It was better than 5-fluorouracil. In addition, compounds 40b, 40d, and 40e presented good inhibitory performance against SGC-7901 with the IC_{50} between 8.64 and 11.46 μM, which were better than 5-fluorouracil (Fig. 6).

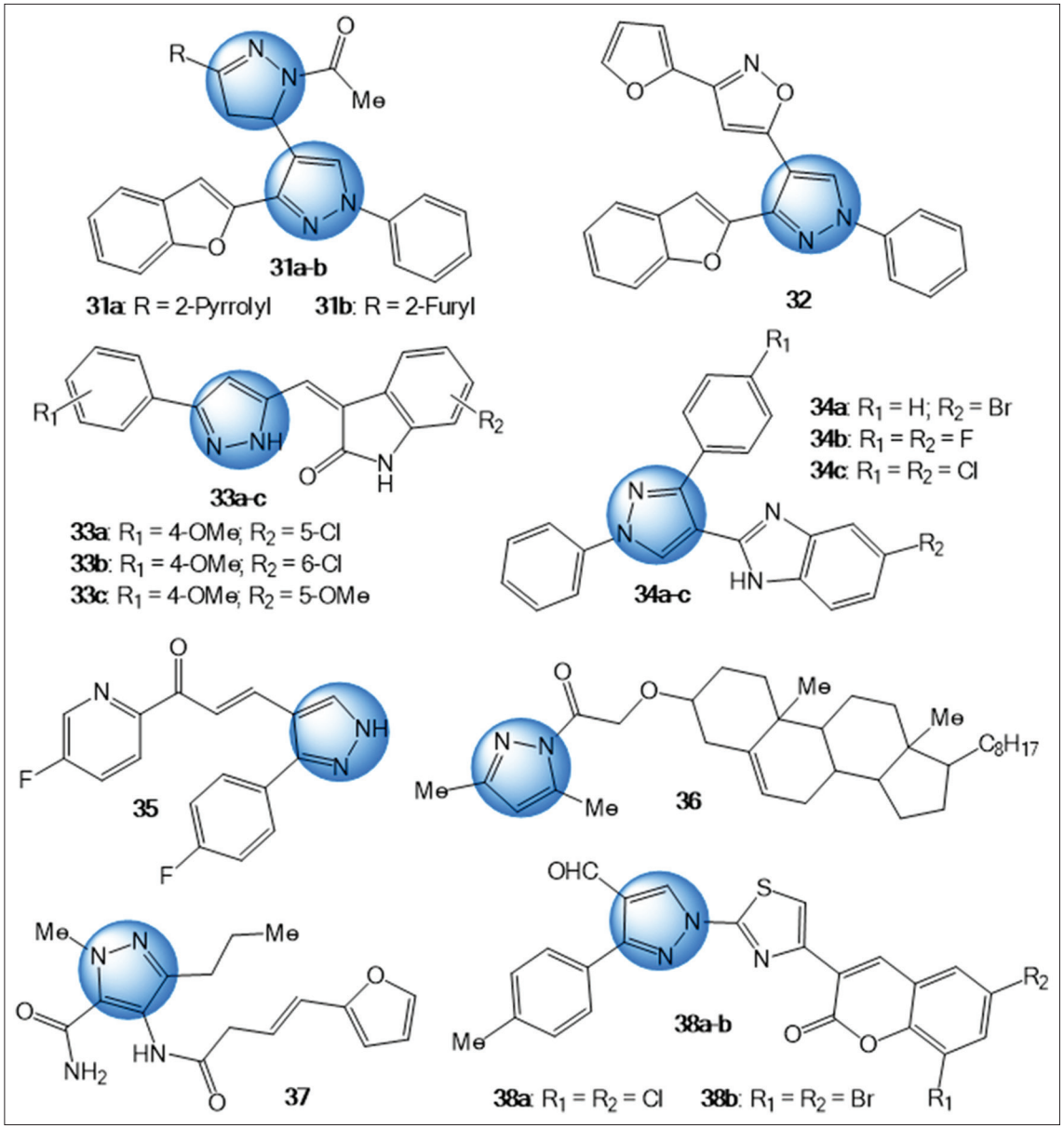

Fig. 5: Pyrazole derivatives discovered during the year 2015

Hafez *et al*. investigated the synthesis of novel pyrazole derivatives decorated with oxa/thiadiazolyl, pyrazolyl moieties, and pyrazolo[4,3-d] pyrimidines as potential anticancer agents [38]. Among the designed compounds, compounds 41a, 41b, and 42 indicated higher anticancer activity than doxorubicin as standard drug. A novel series of 6-aryl-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-ones were prepared by Rahmouni *et al*. in a single step through the reaction of carboxamide with several aromatic aldehydes in the presence of iodine [39]. From the results, it was monitored that compound 43 had the highest cytotoxicity against HCT-116 and MCF-7 cancer cell lines at 100 µM with % inhibition values of 75.4 ± 8.9 and 72.0 ± 4.9%, respectively. To the various products evaluated, the HCT-116 colon cell line is more sensitive than MCF-7 breast cancer cell line. In another research, the development of a small library of 1-acetyl-5-aryl-4,5-dihydro-1H-pyrazoles (44a-g) was described by Ratković *et al*. [40]. Further, it was noted that compounds 44c, 44d, and 44g were the most selective inhibitor of HCT-116 cell line. 30 compounds in the series of (Z)-1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-(phenylamino)prop-2-en-1-ones were synthesized by Reddy *et al*. and were investigated against HT-29, PC-3, A-549, U87MG, and HaCaT cancer cell lines [41]. The compounds 45a-c exhibited an excellent and broad spectrum of growth inhibition on all the tested cancer cells with IC_{50} values in the range of 1.25-3.98 µM. A novel series of selective inhibitor for HGC-27, PC-3, EC-109, and MCF-7 was developed by Wang *et al*. [42]. Indolyl substituted 1,4,6,7-tetrahydropyrano[4,3-c]pyrazoles were synthesized, and from bioactivity studies, it was found that compounds 46a and 46b were the most selective to inhibit MCF-7 cell line with activity close to that of doxorubicin. Compound 46c selectively inhibited the growth of HGC-27 and PC-3 cell lines, whereas compound 46d was the most potent for the EC-109 inhibitor.

CONCLUSION AND FUTURE PROSPECT

The main goal of this review is focused on pyrazole heterocyclic ring decorated with various functional groups. These compounds displayed a large spectrum of biological performance, especially as anticancer agents. Some of them were selective for certain cancer cell line with activity greater than reference drugs. The design and development of anticancer agents become an interesting field of research since cancer

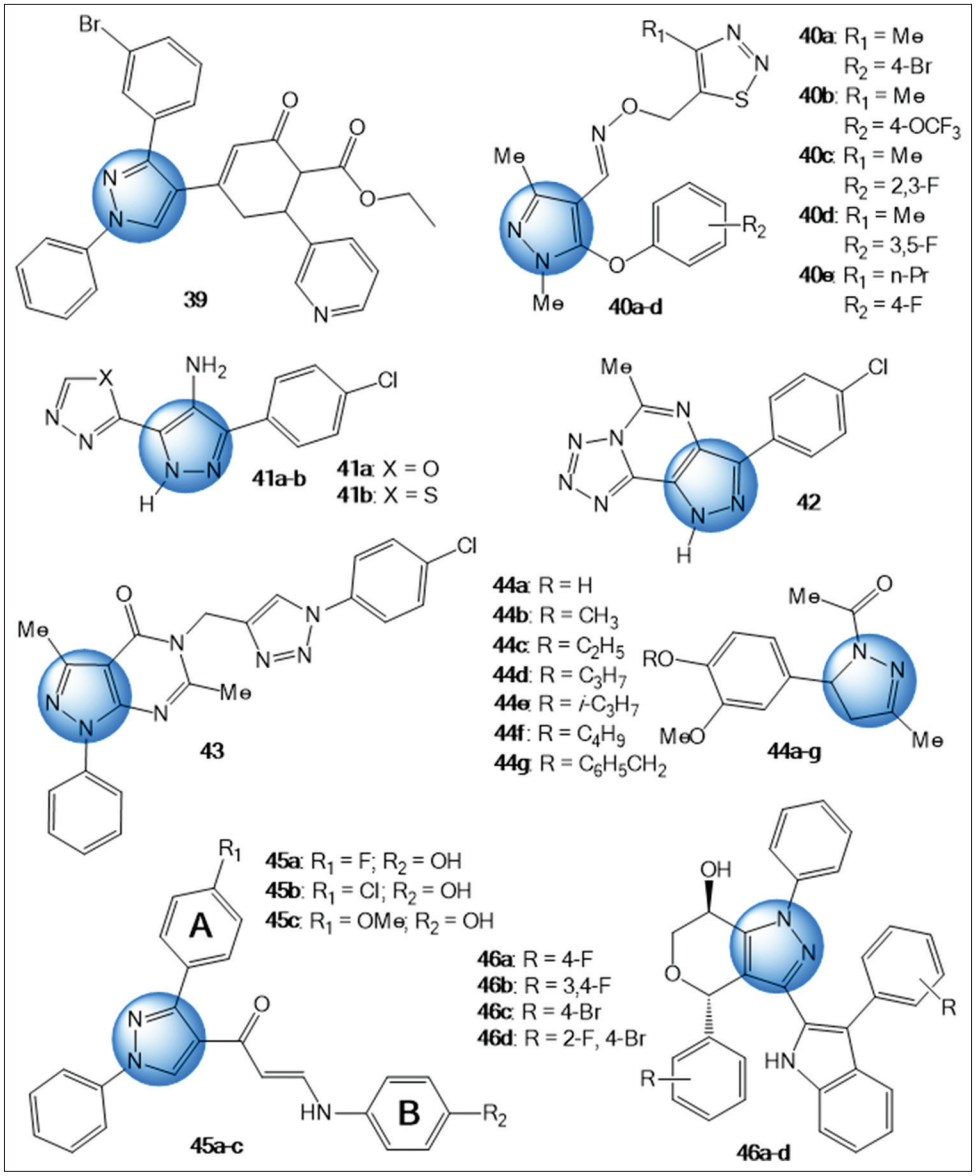

Fig. 6: Pyrazole derivatives discovered during the year 2016

is the deadly disease in the world. In future, we hope researchers will explore new candidates for anticancer through the green organic synthesis of functional molecules.

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