JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Pyrazole as versatile chemotherapeutic agents: A Review

Aga Mansoor, Tazeem*, Mazhar Mehdi, S. Jamal Haider Zaidi
Department of Chemistry, Shia P. G. College, Lucknow
*Corresponding author's Email id: tazeem.chem09@gmail.com

Abstract: Pyrazoles are well known for their therapeutic effect and well document in literature. This study focuses on the resent development of Pyrazoles derivatives and their biological activities such as antimicrobial, antifungal, anti-inflammatory and antitumor activity. This review provides collective information about substituted/fused ring pyrazole system and highlights some examples of pyrazole containing chemotherapeutic substances in the current literature.

Key words: Pyrazole, antimicrobial, antifungal, anti-inflammatory and antitumor activity.

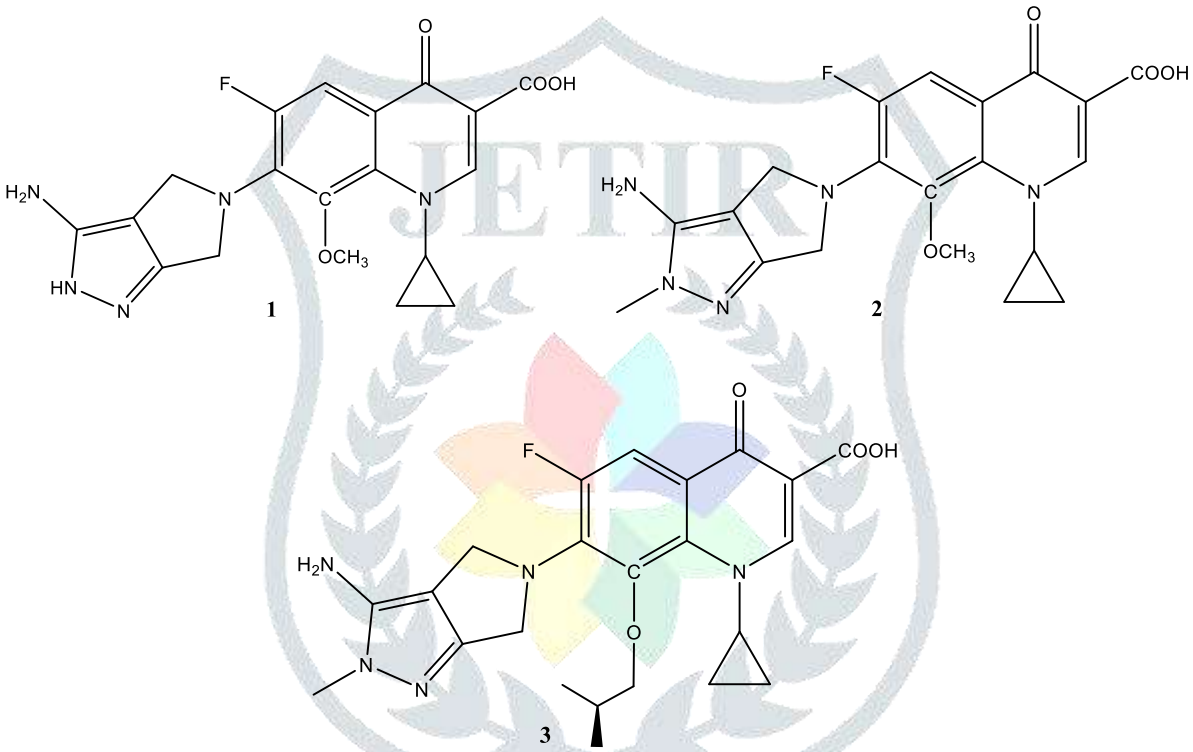
Introduction:

In the literature exploration of wide variety of heterocyclic compounds have been done for the development of potential biologically active compounds. Among these heterocyclic compounds, pyrazoles ring with different substitution considered as one of the key compound that are known for their various chemotherapeutic activity such as antimicrobial,[1,2] antifungal,[3] and antiviral agents.[4]. Moreover, there are large number of fused ring pyrazole derivatives are well documented in history having various antileukemic,[5] antitumor[6,7] and antiproliferative[8,9] activities. Pyrazole derivatives also have considerable importance due to the practical application in field of agriculture science [10, 11]. Phenylpyrazole based fipronil and its analogs are widely used as insecticides for plant protection (crops, vegetables, fruits) and also used as biocides for invertebrate pest control in fish farming. [12]

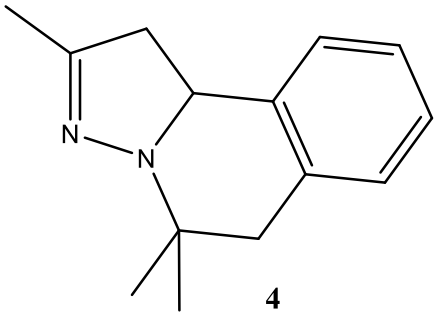
In this review, we address pyrazole based compounds having different chemotherapeutic activity such as antibacterial, antifungal, anti-inflammatory and anticancer activity.

Anti-bacterial and Antifungal activity:

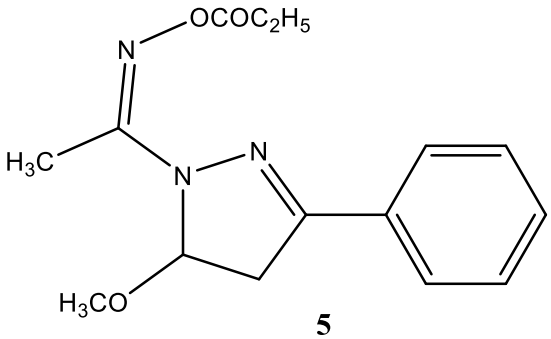
Xin Guo et al. developed a series of novel 7-(3-amino-(2-methyl-)pyrrolo[3,4-c]-pyrazol-5(2H,4H,6H)-yl)fluoroquinolone derivatives. These newly developed compounds were evaluated for their antibacterial activity against *Staphylococcus aureus* including MRSA, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Results reveal that most of the target compounds have good activity against *S. aureus* including MRSA and *S. epidermidis* including MRSE. Compounds **1**, **2** and **3** showed similar potencies as reference drug gemifloxacin. [13]



Xin-Hua Liu et al. reported a series of novel 1-(5-substituted-3-substituted-4,5-dihydropyrazol-1-yl)ethanone oxime ester derivatives. All the compounds screened for their antibacterial activity against *B. subtilis* ATCC 6633, *Escherichia coli* ATCC 35218, *P. fluorescens* ATCC 13525, and *S. aureus* ATCC 6538. The results show that compounds **4** and **5** can strongly inhibit *Staphylococcus aureus* DNA gyrase and *Escherichia coli* DNA gyrase. [14]

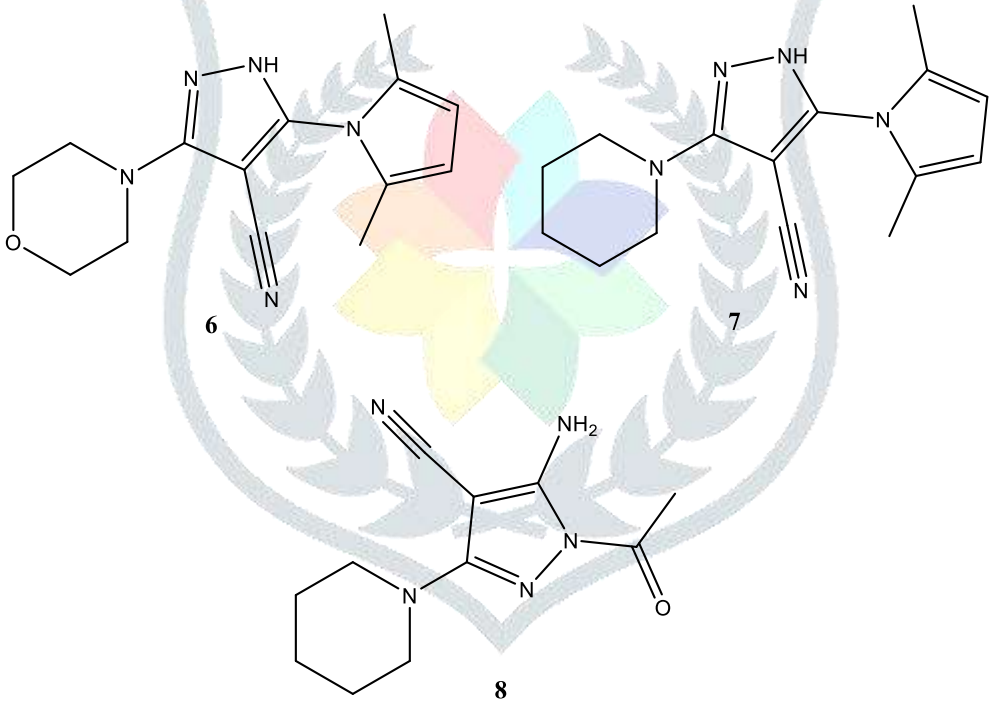


4



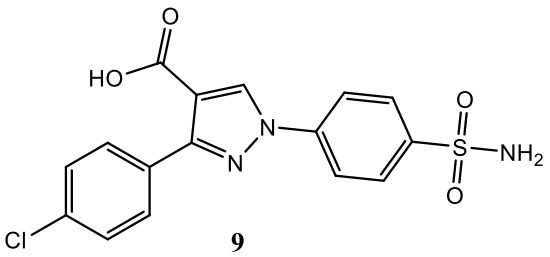
5

Wedad M. Al-Adiwish et al. reported the synthesis of pyrazolo[1,5-a]pyrimidine and pyrazolo[5,1-c][1,2,4]triazine derivatives and screened for their antibacterial activity. Most of the compounds show inhibitory effect against bacteria including MRSA, *S. epidermidis*, *E. faecalis*, *B. subtilis* and *S. typhimurium.* Compounds **6** and **7** showed pronounced antibacterial activity against *B. subtilis.* Whereas **8**, has greater inhibitory activity toward *B. subtilis*, *S. aureus,* and *E. coli*. [15]

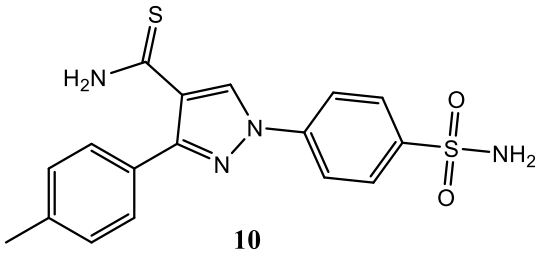


Pawan K. Sharma et al. synthesized pyrazole-4-carboxylic acids and carbothioamides and evaluated for their in vitro antibacterial activity against four pathogenic bacterial strains namely, *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive), *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative) and in vitro antifungal activity against two pathogenic fungal strains namely, *Aspergillus niger* and *Aspergillus flavus*. Three tested

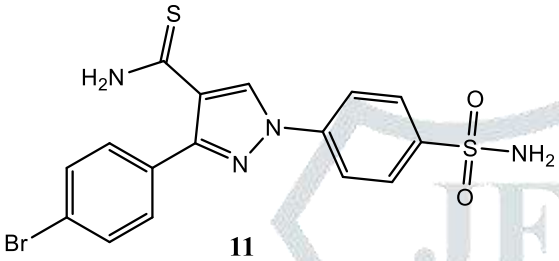
compounds, **9, 10** and **11** exhibited moderate antibacterial activity against Gram-positive bacteria and **12** showed moderate antifungal activity against the tested fungi. [16]



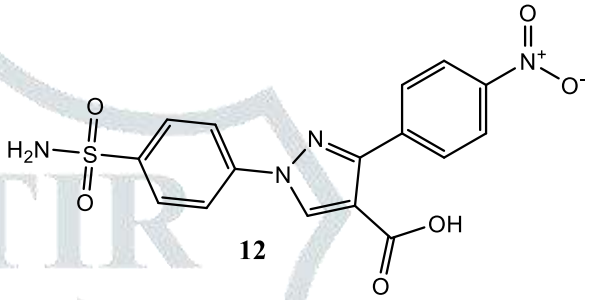
9



10

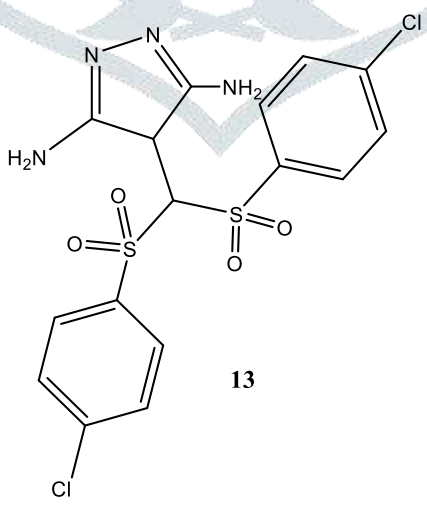


11



12

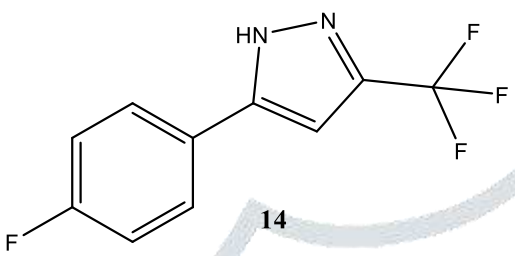
A. Padmaja et al. reported a series of a substituted pyrazole derivatives, all compounds were synthesized from Michael adducts, 2-(1,2-diaroylethyl)malononitrile and 2-(1,2-diarylsulfonylethyl)malononitrile by cyclocondensation reaction with suitable nucleophile. All the target compounds were evaluated for their antimicrobial and antioxidant activities. The results of preliminary antibacterial data revealed that, compounds **13** exhibited maximum activity against Grampositive bacteria with inhibitory zone >30 mm and good activity against Gram-negative bacteria (inhibitory zone >25 mm).[17]



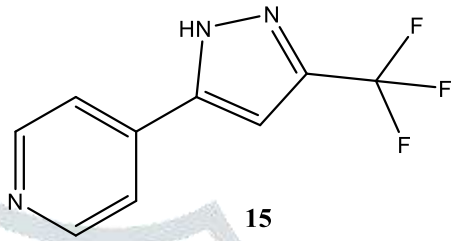
13

Dun-Jia Wang et al. reported several new trifluoromethyl-1H-pyrazoles by reaction of hydrazine monohydrate with 1,3-diketones. All structures were established on the basis of elemental analysis, IR, 1H NMR and EI-MS

spectroscopy data. These newly synthesized compounds were subject for their anti-microbial activities by disc diffusion method against *Escherichia coli*, *Staphylococcus aureus*, *Pyricularia oryzae* and *Rhizoctnia solani*. Most of the trifluoromethyl-1H-pyrazoles derivatives exhibited a certain degree of anti-bacterial and anti-fungal activities. Compound **14** and **15** exhibited slightly higher activities against *E. coli*, *S. aureus*, *P. oryzae* and *R. solani* as compared to other derivatives. [18]



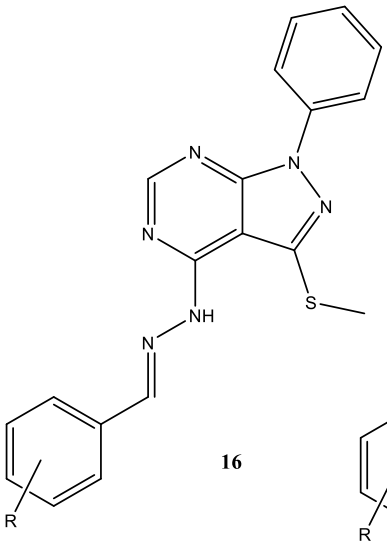
14



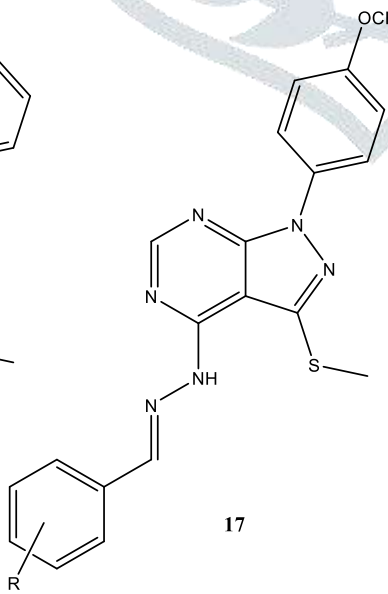
15

Anticancer activity:

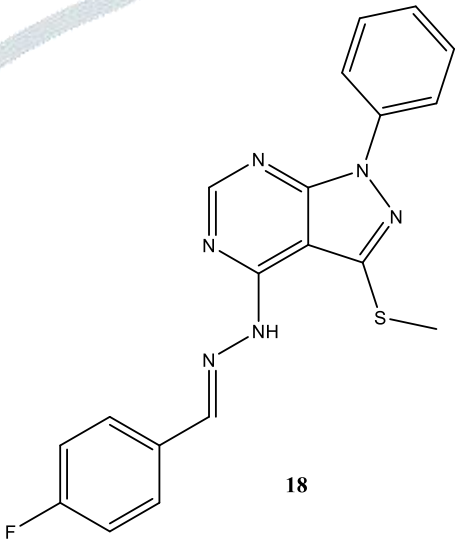
M. K. A. El Hamid et al. synthesized a series of new 1-aryl-4-benzylidenehydrazinyl-3-methylsulphanyl-pyrazolo[3,4-d]pyrimidines derivatives. These compounds screened for their cytotoxic activity against human breast cancer cell line, MCF7. Most of the test compounds showed potent antitumor activity comparable to reference drug doxorubicin. SAR study showed that the 1-phenyl substituted series **16** exhibited better antitumor activity than 1-(4-methoxyphenyl) substituted series **17**. It is also noted that compound (**18**) found to have most potent activity among the test compounds with IC_{50} equal to 7.5 nM.[19]



16

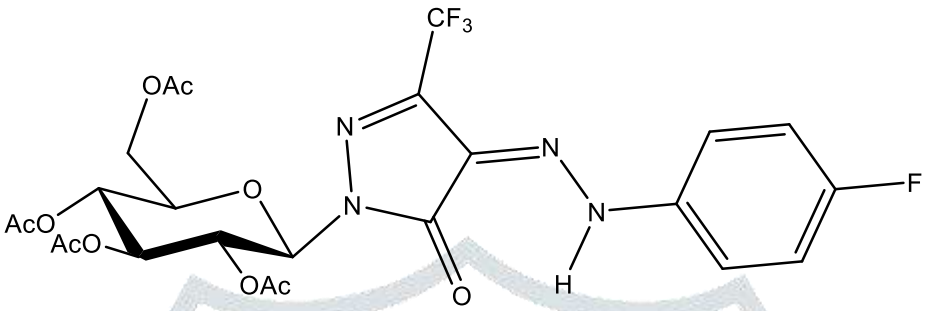


17



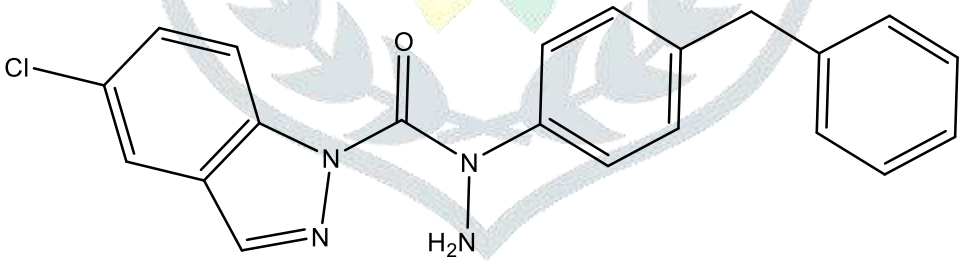
18

Ibrahim M. Abdou et al. reported a new series of 2,4-Dihydropyrazole glucoside derivatives. All these compounds were tested for their antitumor activity towards human promyelotic leukemia (HL60) cell line. Glucoside (**19)**, exhibits better in vitro biological activities with IC_{50} value of 16.4 μM against proliferation of the human promyelotic leukemia (HL60) cell line. [20]



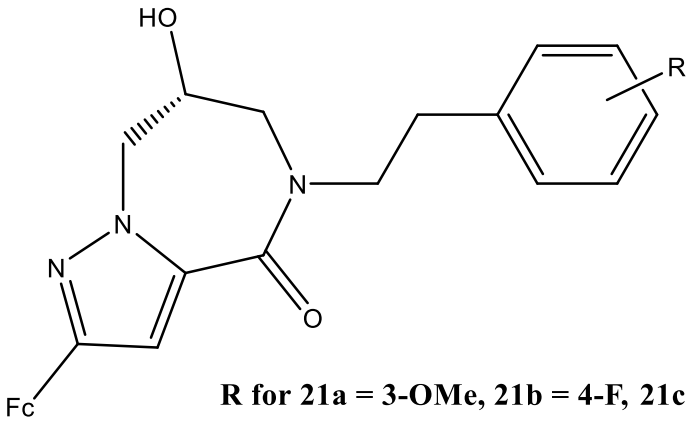
19

Benedetta Maggio et al. reported the synthesis of substituted 3-amino-N-phenyl-1H-indazole-1-carboxamides. Some of synthesized compounds were evaluated for their in vitro antiproliferative activity against leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cell lines. Preliminary data showed that some of the compound was able to inhibit cell growth**.** Among these Compound **20**, found to be the most active compound of the series, showing GI_{50} values in the 0.041-33.6 mM range.[21]



20

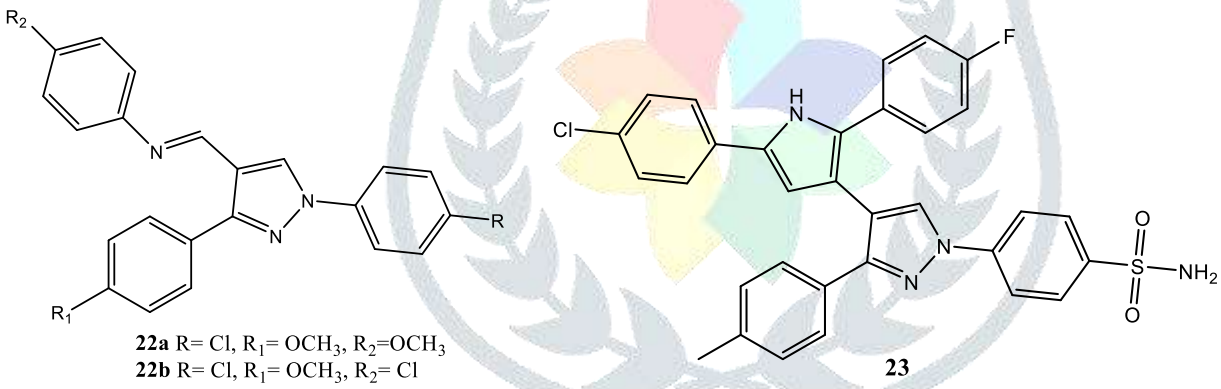
Shi-Li Shen et al. reported a series of novel chiral ferrocenylpyrazolo[1,5-a][1,4]diazepin-4-one derivatives. All the compounds subjected for their preliminary biological activity against A549, H322 and H1299 lung cancer cells. Results of tested compounds revealed that the compound, **21a-c** were more effective against A549 cell. Whereas these compounds also inhibited growth of H1299 and H322 cells by inducing apoptosis. According to SAR study the anti-tumor activities of these compounds also depends upon the nature of substituents present on benzene moiety. [22]



R for 21a = 3-OMe, 21b = 4-F, 21c = 2-F

Anti-inflammatory activity:

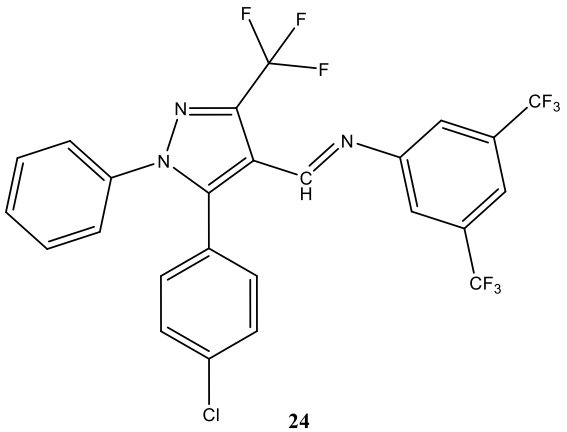
Fatma A. Ragab et al. reported the synthesis of some novel 1,3,4-trisubstituted pyrazoles derivatives and screened for their anti-inflammatory and analgesic activities as well as their ulcerogenic liability. Anti-inflammatory and analgesic activities results showed that most of the compounds have significant GIT tolerance as compared to the standard drug phenylbutazone. These three compounds **22a**, **22b**, and **23** showed high anti-inflammatory activity and good analgesic activity. [23]



22a R= Cl, R_1= OCH_3, R_2=OCH_3
22b R= Cl, R_1= OCH_3, R_2= Cl

23

Magda A.-A. El-Sayed et al. synthesized new pyrazole and pyrazoline derivatives and evaluated for their ability to inhibit ovine COX-1/COX-2 isozymes. Among the tested compound 8d exhibit optimal COX-2 inhibitory potency (IC_{50} = 0.26 μM) and selectivity (SI) = >192.3] as compare with reference drug celecoxib (IC_{50} value of 0.28 μM and selectivity index of 178.57). Furthermore, the anti-inflammatory activity of newly synthesized compounds were also investigated and some compounds possess potent anti-inflammatory activity (61–89% reduction in inflammation). Compound **24** showed the highest anti-inflammatory activity among the tested compounds with ED_{50} of 0.170 mmol/ as compared to diclofenac and celecoxib (ED_{50} = 0.198 and 0.185 mmol/kg, respectively. [24]



24

References:

[1] Holla, B.S., Mahalinga, M., Karthikeyan, M.S., Akberali, P.M. and Shetty, N.S., Synthesis of some novel pyrazolo[3,4-d]pyrimidine derivatives as potential antimicrobial agents, Bioorg. Med. Chem. 14 (2006) 2040-7

[2] Shamroukh, A.H., Zaki, M.E.A., Morsy, E.M.H., Abdel-Motti, F.M. and Abdel-Megeid, F.M.E., Synthesis, isomerization, and antimicrobial evaluation of some pyrazolopyranotriazolopyrimidine derivatives, Arch. Pharm. Chem. Life Sci. 340: (2007) 345-51.

[3] Akbas, E. and Berber, I., Antibacterial and antifungal activities of new pyrazolo[3,4-d]pyridazin derivatives, Eur. J. Med. Chem. 40: (2005) 401-5.

[4] Yan, R.Z., Liu, X.Y., Xu, W.F., Pannecouque, C., Witvrouw, M. and De Clercq, Synthesis and anti-HIV evaluation of the novel 2-(m-chlorobenzyl)-4-substituted-7-methyl-1, 1, 3-trioxo-pyrazolo[4, 5-e] [1, 2, 4]thiadiazines, E., Arch. Pharm. Res. 29 (2006) 957-62

[5] Chou, L.C., Huang, L.J., Yang, J.S., Lee, F.Y., Teng, C.M. and Kuo, S.C., Synthesis of furopyrazole analogs of 1-benzyl-3-(5-hydroxymethyl-2-furyl)indazole (YC-1) as novel anti-leukemia agents, Bioorg. Med. Chem. 15 (2007) 1732-40.

[6] Li, J., Zhao, Y.F., Zhao, X.L., Yuan, X.Y. and Gong, P., Synthesis and anti-tumor activities of novel pyrazolo[1,5-a]pyrimidines, Arch. Pharm. Chem. Life Sci. 339 (2006) 593-7.

[7] Krystof, V., Moravcova, D., Paprskarova, M., Barbier, P., Peyrot, V., Hlobilkova, A., Havlicek, L. and Strnad, M., Synthesis and biological activity of 8-azapurine and pyrazolo[4,3-d]pyrimidine analogues of myoseverin. Eur. J. Med. Chem. 41 (2006) 1405-11.

[8] Schenone, S., Bruno, O., Ranise, A., Bondavalli, F., Brullo, C., Fossa, P., Mosti, L., Menozzi, G., Carraro, F., Naldini, A., Bernini, C., Manettic, F. and Botta, M., New pyrazolo[3,4-d]pyrimidines endowed with A431 antiproliferative activity and inhibitory properties of Src phosphorylation, Bioorg. Med. Chem. Lett. 14 (2004) 2511-7.

[9] Daidone, G., Raffa, D., Maggio, B., Raimondi, M. V., Plescia, F. and Schillaci, D., Synthesis and antiproliferative activity of triazenoindazoles and triazenopyrazoles: a comparative study Eur. J. Med. Chem. 39 (2004) 219-24.

[10]. W.E Krikpatrick; T Okabe; I.W Hillyard; R.K Robins; A.T Dren; T.J Novinson, 3-Halo-5,7-dimethylpyrazolo [1,5-a]pyrimidines, a nonbenzodiazepinoid class of antianxiety agents devoid of potentiation of central nervous system depressant effects of ethanol or barbiturates *Med. Chem*.**,** 20 (1977**)** 386-93.

[11]. A. A. Elagamy;.F.M.A. E1- Taweed ; F. A Amer; H.H Zoorobs. *Arch, pharm*. **1987,** 246, 320.

[12] N. Simon-Delso, V. Amaral-Rogers, L. P. Belzunces, J. M. Bonmatin, M. Chagnon, C. Downs, L. Furlan, D. W. Gibbons, C. Giorio, V. Girolami, D. Goulson, D. P. Kreutzweiser, C. H. Krupke, M. Liess, E. Long, M. McField, P. Mineau, E. A. D. Mitchell, C. A. Morrissey, D. A. Noome, L. Pisa, J. Settele, J. D. Stark, A. Tapparo, H. Van Dyck, J. Van Praagh, J. P. Van der Sluijs, P. R. Whitehorn, M. Wiemers, Systemic insecticides (neonicotinoids and fipronil): trends, uses, mode of action and metabolites, Environ Sci Pollut Res 22 (2015) 5–34.

[13] Xin Guo, Yi Liang Li, Yu Fei Liu, Hui Yuan Guo, Yu Cheng Wang, Synthesis and in vitro antibacterial activities of 7-(3-aminopyrrolo[3,4-c]pyrazol-5(2H,4H,6H)-yl)quinolone derivativesChinese Chemical Letters 21 (2010) 1141–1144.

[14] Xin-Hua Liu, Pin Cui, Bao-An Song, Pinaki S. Bhadury, Hai-Liang Zhua and Shi-Fan Wang, Synthesis, structure and antibacterial activity of novel 1-(5-substituted-3-substituted-4,5-dihydropyrazol-1-yl)ethanone oxime ester derivatives, Bioorganic & Medicinal Chemistry 16 (2008) 4075–4082.

[15] Wedad M. Al-Adiwish, M.I.M. Tahir, A. Siti-Noor-Adnalizawati, Siti Farah Hashim, Nazlina Ibrahim, W.A. Yaacob, Synthesis, antibacterial activity and cytotoxicity of new fused pyrazolo [1,5-a]pyrimidine and pyrazolo[5,1-c][1,2,4]triazine derivatives from new 5-aminopyrazoles, European Journal of Medicinal Chemistry 64 (2013) 464-476.

[16] Pawan K. Sharma, Navneet Chandak, Pawan Kumar, Chetan Sharma, Kamal R. Aneja. Synthesis and biological evaluation of some 4-functionalized-pyrazoles as antimicrobial agents. European Journal of Medicinal Chemistry 46 (2011) 1425-1432.

[17] A. Padmaja, T. Payani, G. Dinneswara Reddy, V. Padmavathi, Synthesis, antimicrobial and antioxidant activities of substituted pyrazoles, isoxazoles, pyrimidine and thioxopyrimidine derivatives. European Journal of Medicinal Chemistry 44 (2009) 4557–4566.

[18] Dun-Jia Wang, Ling Fan, Chun-Yang Zheng, Zheng-Dong Fang, Synthesis and anti-microbial activity of some new fluorinated 1H-pyrazoles. Journal of Fluorine Chemistry 131 (2010) 584–586.

[19] Mohammed K. Abd El Hamid, Marko D. Mihovilovic, Hala B. El-Nassan, Synthesis of novel pyrazolo[3,4-d]pyrimidine derivatives as potential anti-breast cancer agents European Journal of Medicinal Chemistry 57 (2012) 323-328.

[20] Ibrahim M. Abdou, Ayman M. Saleh and Hussein F. Zohdi, Synthesis and Antitumor Activity of 5-Trifluoromethyl-2,4-dihydropyrazol-3-one Nucleosides, Molecules 2004, 9, 109–116.

[21] Benedetta Maggio, Maria Valeria Raimondi, Demetrio Raffa, Fabiana Plescia, Stella Cascioferro, Salvatore Plescia, Manlio Tolomeo, Antonietta Di Cristina, Rosaria Maria Pipitone, Stefania Grimaudo, Giuseppe Daidone, Synthesis of substituted 3-amino-N-phenyl-1H-indazole 1-carboxamides endowed with antiproliferative activity. European Journal of Medicinal Chemistry 46 (2011) 168-174.

[22] Shi-Li Shen, Jin-Hui Shao, Ji-Zhuang Luo, Jin-Ting Liu, Jun-Ying Miao, Bao-Xiang Zhao, Novel chiral ferrocenylpyrazolo[1,5-a][1,4]diazepin-4-one derivatives e Synthesis, characterization and inhibition against lung cancer cells, European Journal of Medicinal Chemistry 63 (2013) 256-268.

[23] Fatma A. Ragab, Nagwa M. Abdel Gawad, Hanan H. Georgey, Mona F. Said, Synthesis of novel 1,3,4-trisubstituted pyrazoles as anti-inflammatory and analgesic agents, European Journal of Medicinal Chemistry 63 (2013) 645-654.

[24] Magda A.-A. El-Sayed, Naglaa I. Abdel-Aziz, Alaa A.-M. Abdel-Aziz, Adel S. El-Azab,

Kamal E.H. ElTahir, Synthesis, biological evaluation and molecular modeling study of pyrazole and pyrazoline derivatives as selective COX-2 inhibitors and anti-inflammatory agents. Part 2, Bioorganic & Medicinal Chemistry 20 (2012) 3306–3316.