HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 2: (3), 2012, 349-359**

PYRAZOLE: BIOLOGICALLY ACTIVE SUBSTANTIAL COMPONENT

V. Sareen*, V. Khatri and S. Sareen

Department of Chemistry, University of Rajasthan, Jaipur
E-mail: sareen_s297@yahoo.com

Heterocyclic compounds are cyclic compounds in which the ring atoms are of carbon and some other element called as hetero atoms (e.g. N, S, O etc). Among five membered heterocyclic compounds containing two hetero atoms, pyrazole is one of the most important in medicinal chemistry with regard to its wide spreaded biological importance. The simple doubly unsaturated compound containing two nitrogen and three carbon atoms in the ring, with the nitrogen atoms neighbouring, is known as pyrazole. The reduction products are pyrazoline and pyrazolidine. Several pyrazoline substitution products are used in medicine. Many of these are derivatives of 5-pyrazolone. Some can be related to 3,5-pyrazolidinedione. For a long time no pyrazole derivative had been found in nature, but in 1959 -(1-pyrazolyl) alanine was isolated from the seeds of water melons (Citurllus lanatus) (L. Fowden).

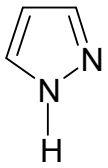


FIGURE 1

Pyrazoles are well established in literature as important biologically active heterocyclic compounds. These derivatives are the subject of many research studies due to their wide spread potential biological activities. Literature survey revealed that pyrazole derivatives possess diverse pharmacological activities:

I. ANTITUMOR ACTIVITY

An antitumor agent is one that counteracts or prevents the formation of malignant tumors. Abdel-Rahman Farghaly [1] synthesized a series of new [1-(4-methoxybenzyl)indol-3-yl](1*H*-pyrazol-1-yl)methanones,1-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl)-3-subsituted-1*H*-pyrazol-5(4H)-ones using the 1-(4-methoxybenzyl)-1*H*-indole-3-carbohydrazide as a key intermediate. The target compounds were tested *in-vitro* for tumor cell-growth inhibition.

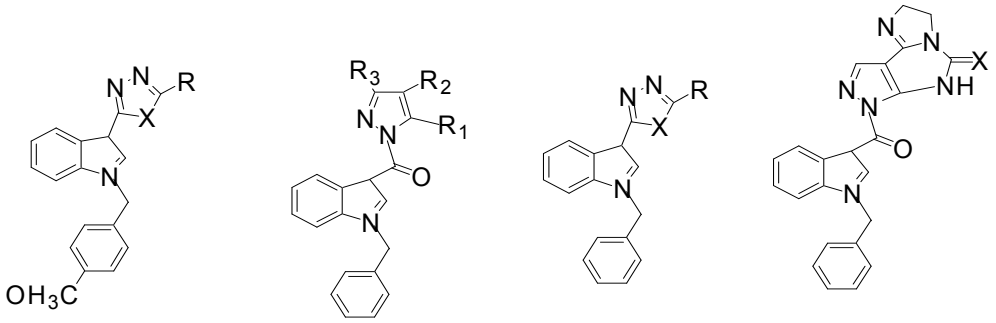
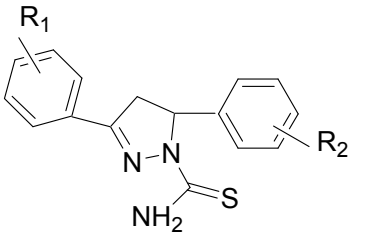


FIGURE 2

Mohammed S. M. Al-Saadi [2] synthesized and did *in vitro* antitumor activity of some fused pyrazole and pyrazoline ring systems. Compounds proved to be the most active antitumor agent in the present study with GI50, TGI and LC50 MG-MID values of 8.12, 25.7 and 69.2 μM, respectively, with high sensitivity towards leukaemia, melanoma and renal cell lines.

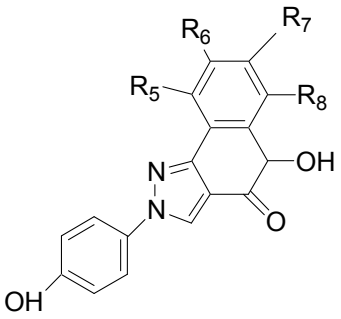
Peng-cheng LV ***et al.*** [3] synthesized a series of pyrazole derivatives. The compound (Fig. 3) having R_1= 3, 4- 2CH3 and R_2=4-OCH3 substitution own high antiproliferative activity against MCF-7 with IC50 0.08 μM.



R_1	R_2
3,4-2CH_3	4-OCH_3

FIGURE 3

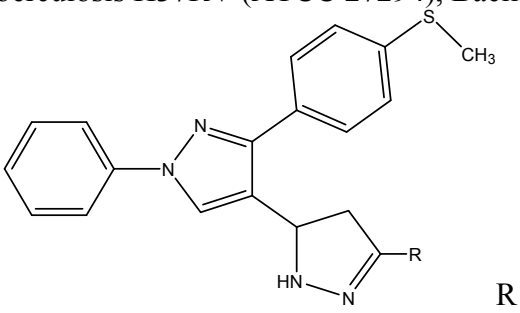
Michael S. Christodoulo (2010) *et al.* [4] synthesized a new series of trisubtituted pyrazole derivatives and screened the compounds for anti-antiangiogenic activity. Compounds containing the fused pyrazole [4,3-c] quinololine motifs emerged as potent anti-angiogenic compounds, which also had the ability to inhibit the growth of human breast (MCF-7) and cervical (Hela) carcinoma cells *in vitro*. Compound **8b** (Fig. 4) were found to be active, eliciting 64% of inhibition ($p<0.01$) by chicken chlorioallantoic membrane (CAM) assay**.**



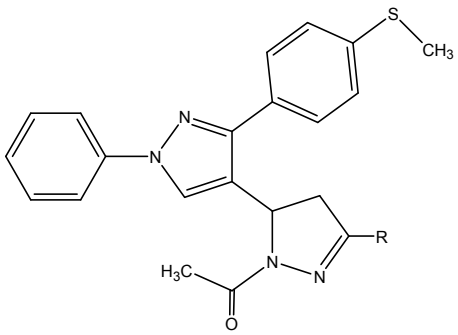
Compounds	R_5	R_6	R_7	R_8
	-H	-OH	-H	-H

FIGURE 4

P. T. Chovatia et al. [5] synthesized 1-acetyl-3,5-diphenyl-4,5 dihydro (1H)pyrazole derivatives [Fig. 5] and studied their antitubercular and antimicrobial inhibitory activity against Mycobacterium tuberculosis H37RV (ATCC 27294), Bacillus Coccous and Aspergillus niger.



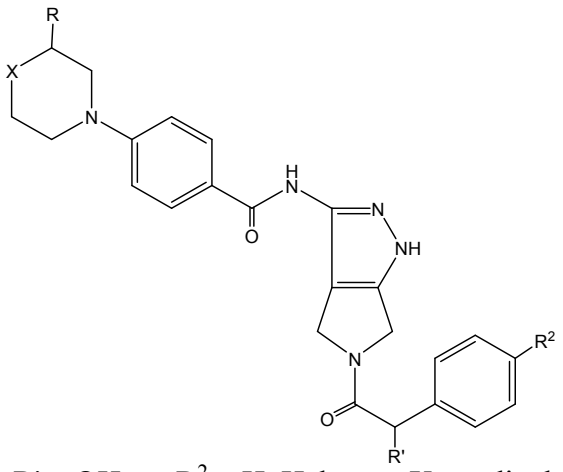
R = C_6H_5, 4-Cl-C_6H_4



R = C_6H_5, 4-Br-C_6H_4

FIGURE 5

Fancelli Daniele et al. [6] prepared pyrazolo [3,4-c] [Fig.: 6] pyrazole derivatives and reported that compounds are useful for treating cell proliferative disorders caused by an altered protein kinase activity including cancer, alzheimer's disease, viral infection, autoimmune diseases and neurodegenerative disorders.



R = H, Me	R' = OH	R^2 = H, Halo	X = a divalent group selected from CH_2
R = H, Me	R' = OH	R^2 = H, Halo	X = a divalent group selected from CH_2
R = H, Me	R' = OH	R^2 = H, Halo	X = a divalent group selected from CH_2

FIGURE 6

Ronghui Lin et al.[7]synthesized 3, 4-disubstituted pyrazole derivatives. The analogues (Fig. 7 & 8) showed potent and selective cyclindependent kinase inhibitory activities & inhibited invitro cellular proliferation in various human cells.

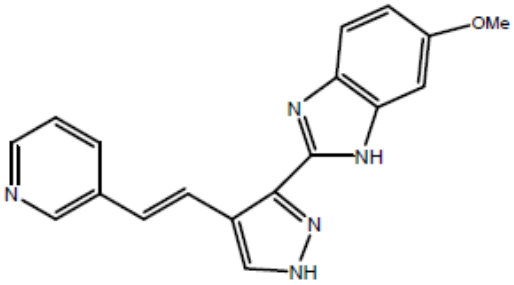


FIGURE 7

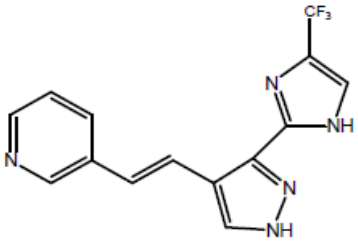


FIGURE 8

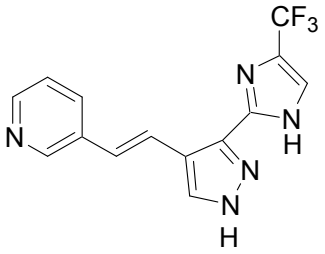
II. ACE-INHIBITORY ACTIVITY

An angiotensin converting enzyme inhibitor is an antihypertensive drug that blocks the formation of angiotensin in the kidney, leading to relaxation of the arteries; promotes the excretion of salt and water by inhibiting the activity of the angiotensin converting enzyme; also used to treat congestive heart failure.

Kantevari S et al.[8] did the synthesis and evaluation of novel 2-butyl-4-chloro-1-methylimidazole embedded chalcones and pyrazoles as angiotensin converting enzyme (ACE) inhibitors. Among the chalcones, three compounds, (E)-3-(2-butyl-4-chloro-1-methyl-1H-imidazol-5-yl)-1-(5-

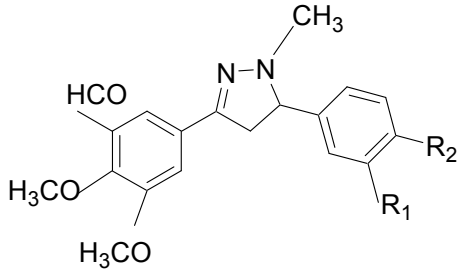
chlorothiophen-2-yl)prop-2-enone, (E)-3-(2-butyl-4-chloro-1-methyl-1H-imidazol-5-yl)-1-(1H-pyrrol-2-yl)prop-2-enone, (E)-3-(2-butyl-4-chloro-1-methyl-1H-imidazol-5-yl)-1-(dibenzo[b,d] thiophen-2-yl)prop-2-enone resulted as most active ACE inhibitors with IC50 of 3.60 μM, 2.24 μM, and 2.68 μM, respectively.

Macro Bonesi *et al*. [9]synthesized a series of pyrazole derivatives (Fig. 9) and investigated their potential activity as Angiotensin-I-converting enzyme inhibitory activity by performing assay. This derivative of pyrazole (Fig. 10) showed effective ACE-inhibitory activity with 0.123 mM IC50 value.



$R_1 = NO_2$

FIGURE 9



$R_2 = OCH_3$

FIGURE 10

III. ANTI MICROBIAL ACTIVITY

An antimicrobial is a chemical that kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans. Antimicrobial drugs either kill microbes (microbiocidal) or prevent the growth of microbes (microbiostatic). Disinfectants are antimicrobial substances used on non-living objects or outside the body.

Gupta et. al. [10] synthesized and carried out the antimicrobial activity of N-substituted pyrazole derivatives. The series of compounds N-substituted -3- benzyl-5-phenylpyrazole are obtained from substituted benzohydrazide. Substituted benzohydrazides are synthesized by the reaction between different methyl benzoate and hydrazine hydrate. The final structures of all compounds were confirmed by FTIR, ^{1}HNMR and Mass spectral data. All the Compounds have been screened for their antimicrobial activity. Salah Abdel Ghaffar Abdel Aziz[11] synthesized and carried out the antimicrobial activities of some novel bispyrazole derivatives containing a hydrophosphoryl unit. Vilsmeier Haack reaction conditions were applied on some methyl ketone aryl phosphonic dihydrazones to yield some interesting bispyrazole derivatives containing a hydrophosphoryl unit. Bis {4-formyl-3-aryl-1*H*pyrazol-1-yl} phosphine oxides were condensed with some nucleophiles such as aniline, phenacyltriphenylphosphonium bromide and 4-phenylthiosemicarbazide followed by treatment with thioglycolic acid, diethyl phosphite and/or acetic anhydride to yield a novel class of bispyrazoles containing sulfur and phosphorus derivatives. Most of the newly synthesized compounds were evaluated for their in vitro antimicrobial activities. Samir Bondock et al.[12] synthesized a series of substituted pyrazole derivatives. The given compound (Fig. 11) was found to exhibit the most potent in-vitro antifungal activity with MICs (6.25 μ/ml) against *A. fumigatus* & *F. Oxysporum* comparable with Chloroamphenicol**.**

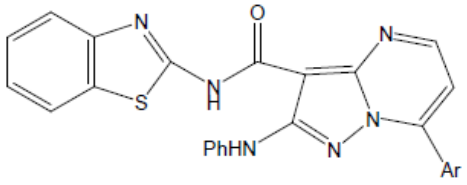


FIGURE 11

Smaail Radi et al.[13] synthesized novel pyrazole derivatives and these derivatives were evaluated for their antimicrobial activity determined by agar plate diffusion technique. Antibacterial activity: against antibacterial strains *Escherichia coli* and determined by agar plate diffusion method. Antifungal activity: against two fungal strains *Saccharomyces cerevisae* and *Fusarium oxysporum f. sp. albicans*.

Streptomycin was used as reference compound in performing antimicrobial assay. These derivatives (Fig. 12) were found to be most potent.

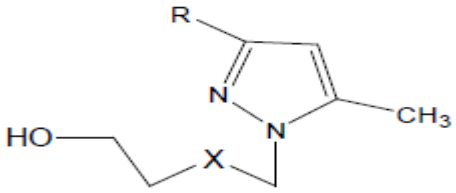


FIGURE 12

Radhakrishnan Sridhar et al.[14] synthesized 1-H Pyrazole carboxylate derivatives and screened for antimicrobial activities.

Antibacterial activity: against four human pathogenic bacteria, *Escherichia coli*, *Pseudomonas aeuroginosa*, *Enterobacter facecalis* and *Staphylococcus aureus*.

Antifungal activity: against five pathogenic fungi such as, *Rhizochonia solani*, *Fusaricom oxysperum*, *Curuvularia lunata*, *Bipolaris oryzae* and *Alternaria alternata*.These derivatives (Fig. 13 & 14) showed significant antimicrobial activity.

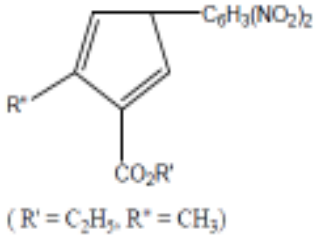


FIGURE 13

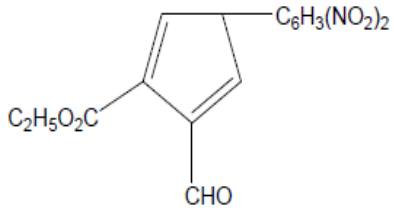


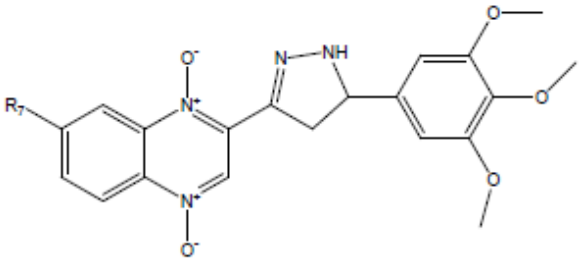
FIGURE 14

IV. ANTI INFLAMMATORY ACTIVITY

S. ARUNKUMAR et al.[15] synthesized and carried out the anti-inflammatory activity of some novel pyrazole derivatives of gallic acid. A new series of [5-substituted-3- (phenylamino)-1*H*-

pyrazol-1yl] (3,4,5 -trihydroxyphenyl)-methanone have been synthesized. 3,4,5-Trihydroxy benzohydrazide was synthesized from propyl gallate and hydrazine hydrate in presence of ethanol. Chalcones were synthesized from acetanilide and various aromatic aldehydes in presence of ethanol and sodium hydroxide solution. By refluxing the compound in presence of ethanol yielded [5-substituted-3-(phenylamino)-4.5-dihydropyrazol-1yl] (3,4,5-trihydroxy phenyl)-methanone. The final compounds [5-substituted-3-(phenylamino)-1*H*-pyrazol-1-yl] (3,4,5-trihydroxyphenyl)-methanone were synthesized by treating compounds with bromine water. The synthesized compounds have been characterized by IR, ^{1}HNMR and Mass spectral data. The compounds were evaluated for anti-inflammatory activity in vivo by carrageenan induced paw edema test. In general all compounds were found to exhibit good anti-inflammatory activity.

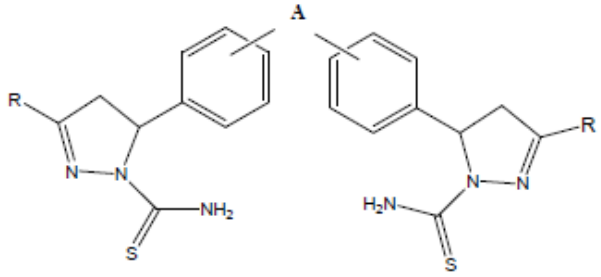
Some of the compounds involving the pyrazole nucleus are useful in treatment and prevention of inflammatory conditions, various pains, collagen diseases, thrombosis, cancer or neurodegenerative diseases.[16] Asuncio´n Burguete et al. [17] synthesized substituted pyrazole derivatives and evaluated them for their anti-inflammatory activities. These derivatives **5a**, **5b** & **5c** showed good anti-inflammatory activity against carrageenan induced rat paw edema test.



Compounds	R_7
5a	H
5b	F
5c	CH_3O

FIGURE 15

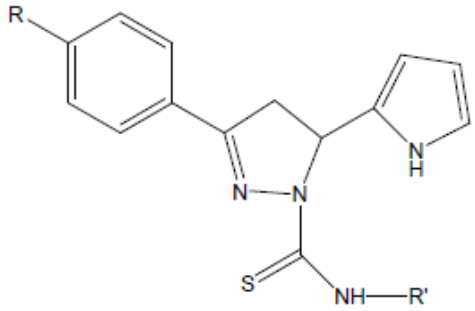
Flora F. Barsoum ***et al*** [18] synthesized bis (3- aryl-4, 5-dihydro-1H Pyrazole-1-thio carboxamide derivatives. The derivative (Fig.16) with substitution, A = 4-O $(CH_2)_2O$-4', R = Ph, showed potent anti- inflammatory activity against carrageenan-induced rat paw edema test.



(A = 4-O$(CH_2)_2$O-4' , R = Ph)

FIGURE 16

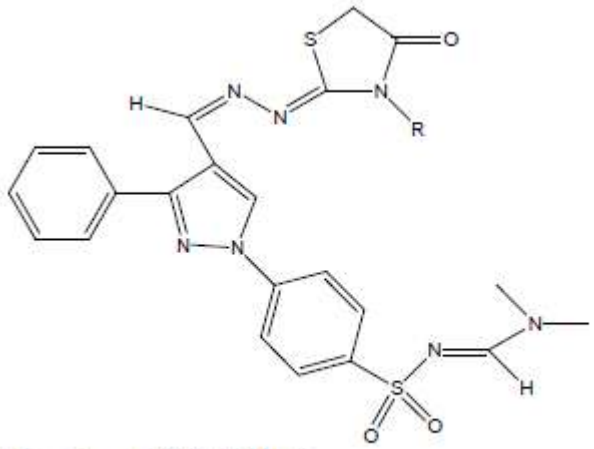
Nesrin Go¨khan-Kelekc et al. [19] synthesized novel pyrazole derivatives, compound **3k** (Fig.17) exhibited anti-inflammatory activity using carrageenan induced paw edema method and acetic acid induced increased capillary permeability comparable to that of indomethacin with no ulcerogenic effect and compound **3k** also showed MAO-B inhibitor activity in mice.



3 k; (R = OCH_3 , R' = C_3H_5)

FIGURE 17

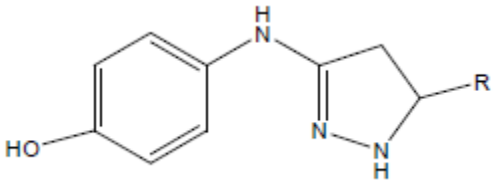
Adnan A. Bekhit et al. [20] synthesized thiazolyl and thaidiazolyl derivatives of 1H-Pyrazole. Potent derivative showed significant anti inflammatory activity by the cotton pellet granuloma method of rat paw edema bioassay. Derivative **3 b** (Fig.18) showed comparable antimicrobial activity to that of ampicillin against *E. coli* .



(3 b; R = 4-$CH_3C_6H_4$)

FIGURE 18

S. K. Sahu et al.[21] synthesized novel pyrazoline derivatives. The derivatives **2c**, **2e** & **2f** showed potent antimicrobial activity: antibacterial activity; by muller hinton agar (Hi-media) plates by agar diffusion cup-plate method for Staphylococcus aureus, Salmonella typhi & E. coli. Antifungal activity was tested on sabouraud dextrose agar plates by cup-plate method against Candida albicans & Aspergillus niger. In both of these assays ciprofloxacin and cotrimazole were used as standard drugs. Also the compounds **2 c** & **2 e** showed effective analgesic (by Tail flick method) and anti-inflammatory (by Carageenan induced rat paw edema method) activities.

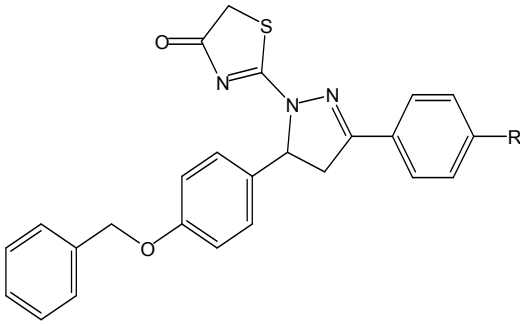


Compounds	R
2c	-4-NO_2-C_6H_4
2e	-2-OH-C_6H_4
2f	-4-Cl- C_6H_4

FIGURE 19

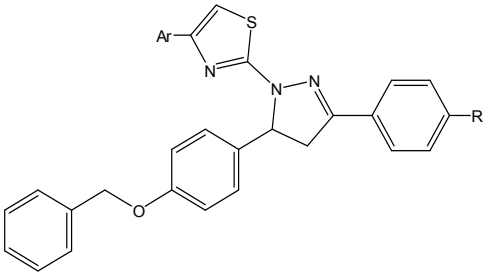
V. ANTIVIRAL ACTIVITY

O.I. El-Sabbagh et al.[22] synthesized new pyrazolo thiazolones [Fig. 20] and pyrazolo thiazoles [Fig. 21] derivatives and evaluated their antiviral activity against vaccinia virus (Lederle strain) in HEL cell cultures with an EC5O value of 7 μg/ml.



R = H, Br, Cl, CH_3

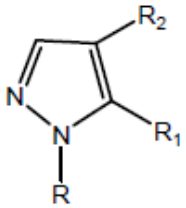
Figure-20



R = H, Br, Cl, CH_3

Figure 21

Aymn E. Rashad et al.[23] synthesized substituted pyrazole derivatives. These derivatives showed promising antiviral activity against hepatitis A virus and Herpes Simplex virus type-1 using plaque infective assay.



R_1	R_2
CN	NH_2
CN	NHCSNHCOPh
NH_2	COOEt

R =

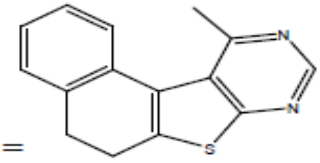


FIGURE 22

VI. ANTICONVULSANT AND ANTIDEPRESSANT ACTIVITY

Mohamed Abdel Aziz *et al.* [24] synthesized novel pyrazole derivatives and screened them for anticonvulsant and antidepressant activities. The derivatives showed comparable antidepressant activity by using tail suspension behavioral despair test and anticonvulsant activity for derivatives by using PTZ induced seizures in mice. Anandarajagopal et al. [25] did the synthesis, characterization and anticonvulsant activity of some pyrazole derivatives. Several number of novel 4-(aryl/substituted aryl) -1-(unsubstituted/aryl/substituted aryl)-3-phenyl-1H-pyrazoles have been synthesized by the reaction of 1-substituted phenyl-3-phenyl-2,3-dibromo prop-1-ones and appropriate unsubstituted and substituted hydrazine in ethanol. 1-substituted phenyl-3-phenyl-2,3-dibromo prop-1-ones were synthesized by the bromination of 1-substituted phenyl-3-phenyl-prop-2-en-1-ones which were synthesized by the reaction of acetophenone with appropriate unsubstituted and substituted aromatic aldehyde. The synthesized compounds were

confirmed by M.P.'s and TLC and their structure was established by various analytical techniques such as IR and ^{1}HNMR spectral studies. The anticonvulsant activity of the synthesized compounds has indicated that all the compounds significantly reduce the electro shock induced convulsions, compared to phenytoin. The pharmacological evaluation may be concluded that the replacement of 1H position of pyrazole with phenyl and substituted phenyl increases the anticonvulsant activity.

Secci D. et al.[26] Monoamine oxidase plays a significant role in the control of intracellular concentration of monoaminergic neurotransmitters or neuromodulators and dietary amines. The rapid degradation of these molecules ensures the proper functioning of synaptic neurotransmission and is critically important for the regulation of emotional and other brain functions. The development of human MAO inhibitors led to important breakthroughs in the therapy of several neuropsychiatric disorders. Different families of heterocycles containing 2 or 4 nitrogen atoms have been used as scaffolds for synthesizing selective monoamine oxidase inhibitors, but the early period of the MAO-inhibitors started with hydrazine derivatives. Pyrazole, pyrazoline, and pyrazolidine derivatives can be considered as a cyclic hydrazine moiety. This scaffold also displayed promising antidepressant and anticonvulsant properties as demonstrated by different and established animal models. Diversely substituted pyrazoles, embedded with a variety of functional groups, are important biological agents and a significant amount of research activity has been directed towards this chemical class.

REFERENCES

1. A.R. Farghaly; ***Arkivoc*, 11, 177 (2010).**
2. M. S. M. Al-Saadi; *Saudi Pharmaceut. J.*, **16,** 135 (2008).
3. L.P.Cheng, L.Z. Hai , L.H. Qiu , J. Sun, Y. Zhou; *Bioorg. Med. Chem*., **18**, 4606 (2010).
4. M.S. Christodoulou, L Sandra, K. M.Kasiotis, S.A. Harotounian; *Bioorg. Med. Chem*., **18**, 4338 (2010).
5. P. T. Chovatia, J. D. Akabori, P. K. Kachhodia, P. D. Zalavadia and H. S. Joshi; *J. Serb. Chem. Soc.*, **71**, 713 (2007).
6. F. Daniele, F. Barbara, M. Jurgen, V. Mario and V. Paola; *PCT Int. Appl*., 38 pp. *CODEN PIXXD2 Wo 2005005427 AI 20050120* (2005).
7. R. Lin, G. Chiu, Y. Yu, P.J. Connolly, S. Li, Y. Lu, M. Adams, A. R. F. Pesquera, S. L. Emanuel and L. M. Greenberger; *Bioorg. Med. Chem. Lett.*, **17**, 4557 (2007).
8. S. Kantevari, D. Addla, P.K. Bagul, B. Sridhar, S.K. Banerjee; *Bioorg. Med. Chem*., **19**, 4772 (2011).
9. M. Bonesi, M.R. Loizzo, G.A. Statti, S. Michel, F. Tillequin, Menichini; *Bioorg. Med. Chem. Lett.*, **20**, 1990 (2010).
10. D. P. Gupta, R. S. Bhadauria1, V. Soan; *International J. Pharmaceut. & Applied Sciences***, 1,** 97 (2010).
11. S. A.G. A. Aziz, T. E.S.Ali, K.M.E. Mahdy & S. M. A. Karim; *European J.Chem.,* **2**, 25 (2011).
12. S. Bondock, W. Fadaly, M.A. Metwally.; *European J. Med. Chem*., 227 (2010).
13. S.Radi, S. Salhi, A. Radi; *Lett. in Drug Design & Discovery, Bentham Science Publishers Ltd.*, **7**, 27 (2010).
14. R. Sridhar et al.; *Bioorg. Med. Chem. Lett*., **14,** 6035 (2004).

15. S. Arunkumar, K. Llango, R. S. Manikandan & N. Ramalakshmi; *E-J. Chem.,* **6,** S123 (2009).
16. N. Konishi, K. Nakamura, H. Yamamoto, T. Manabe, Pct. Int. Appl. WO 00 18, 741 (Cl. C07D231/00), 6 Apr.(2000), AU Appl. 1999/2, 243, 16 Aug.1999, 90 pp; Chem. Abstr., **132**, 251149u, (2000).
17. A. Burguete et al.; *Bioorg. Med. Chem. Lett*., **17**, 6439 (2007).
18. F.F. Barsoum, A.S. Girgis; *Eur. J. Med. Chem*., **44**, 2172 (2009).
19. N.G. Kelekc, S.Yabanog˘lu, E. Ku¨peli, U. Salgın et al.; *Bioorg. Med. Chem*., **15**, 5775, (2007).
20. A.A. Bekhit, H.M.A. Ashour, Y.S.A. Ghany, E. Din, A. Baraka; *Eur J. Med. Chem*., **43**, 456 (2008).
21. S.K. Sahu, M. Banerjee, A. Samantray, C. Behera, M.A. Azam; *Tropical J. Pharm. Research*, **7**, 961 (2008).
22. O.I.E. Sabbagh et al.; *Eur. J. Med. Chem.*, **44**, 3746 (2009).
23. A.E. Rashad, M.I. Hegab, R.E. A. Megeid, J.A. Micky and F.M.E.A. Megeid; *Bioorg. Med. Chem*., **16**, 7102 (2008).
24. M. A. Aziz, A.E.Din, G.A. Rahma, A. A.Hassan; *Eur. J. Med. Chem*., **44**, 3480 (2009).
25. A. Kalusalingam, I. Arumugamb, R. Velayutham, U. Natarajan, A. J. S. Johnsamuela, P. Promwichita; *Journal of Global Pharma Technology*, **3**, 25 (2011).
26. D. Secci, A.Bolasco, P. Chimenti and S. Carradori; *Current Med. Chem.*, **18**, 5114 (2011).

Received on June 15,2012.