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SYNTHESIS AND CHARACTERIZATION OF 1-(BENZOYL)-4-(ARYLIDENE)-3-METHYL-1*H*-PYRAZOL-5(4*H*)-ONES DERIVATIVES AND THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT
Pyrazole and its derivatives are considered pharmacologically active and itgives various types of biological activities. The presence of this nucleus in pharmacological agents of diverse therapeutic categories such as a potent anti-inflammatory, anti-microbial, andanalgesic, has proved the pharmacological potential of the pyrazole moiety.
Keywords: Pyrazole Derivatives, Schiff Base, MIC-Bacillus Cereus MTCC 430, E.Coli MTCC 1687, Aspergillus Niger16404.
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INTRODUCTION

Pyrazoles are 5-memberedrings and it is useful in various organic syntheses.Parasols are one of the most studied groups of compounds among the azol[1] family.Pyraole compound in different structures leads to various areas such as medicine, technology, and agriculture. Pyrazole compound give various type of biological activity reported over the years like anti-microbial[2], anti-tumor[3], anti-depressant [4], anti-fungal [5-10]etc.

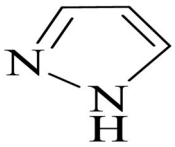

Fig.-1

EXPERIMENTAL

All chemicals used in the synthesis of the titled compounds were of analytical grade. The Melting points were reported by the open capillary tube method and are uncorrected.The reaction was monitored by thin-layer chromatography (TLC) and was carried out on Merck Kieselgel 60 F254 plates. IR spectra were recorded on the Shimadzu FT-IR 8400 using potassium bromide pallets. The 1^H NMR spectra were recorded in DMSO d6 solution in 5 mm tubes at room temperature on a BRUKER 400 MHz FT-NMR with TMS (Tetramethyl silane)as an internal standard. Mass spectra were recorded on SHIMADZU QP-2010. The antimicrobial activity was carried out using the broth dilution method to determine the minimum inhibitory concentration (MIC).

Synthesis of Benzohydrazide (I)

Methyl benzoate (0.22 mol) with hydrazine hydrate (0.22 mol) in methanol at reflux for 7-8 hours. The reaction mixture was cooled, poured into crushed ice, and filtered. Product recrystallized from ethanol. It was filtered, washed with alcohol, and dried. The progress and completion of the reaction were confirmed by TLC. Mobile phase for TLC toluene: acetone (8:2), Yield: 75%, M.P.: 112-114 ˚C.

Synthesis of 1-(Benzoyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (II)

Benzohydrazide (0.01 mol) with ethyl acetoacetate (0.01 mol) in the presence of 20 ml of absolute ethanol, and a catalytic amount of triethylamine (1 ml) at refluxed for 12 hours using a reflux condenser equipped with a magnetic stirrer. After the reaction was complete, the resultant reddish syrup was allowed

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to cool to room temperature. It was washed thoroughly with ether to remove impurities. After the removal of the ether layer, The contents of the reaction mixture were then transferred to crushed ice to obtain precipitates 1-(Benzoyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one. The solid products (II) formed were filtered, washed, and dried. Finally, the products were re-crystallized from alcohol. The progress and completion of the reaction were confirmed by TLC to yield.

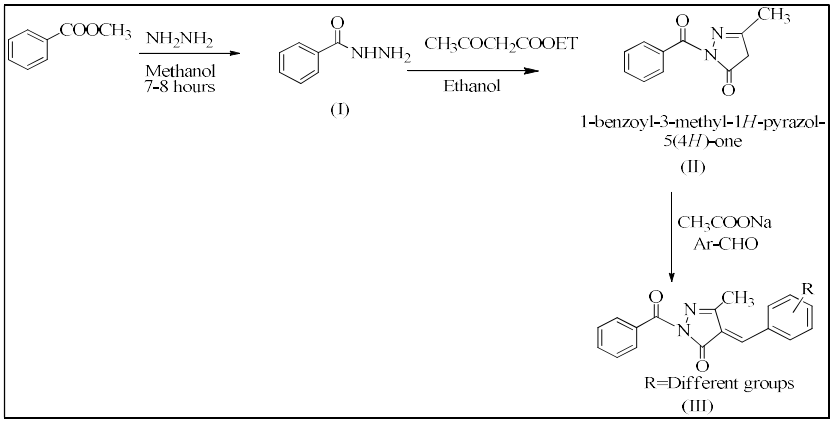

Fig.-2: Reaction Scheme for the Synthesis of the Compounds III(a-n)

Synthesisof 1-(Benzoyl)-4-(arylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (III).

1-(benzoyl)-3-methyl-1*H*-pyrazol-5(4H)-one (0.01 mol) with different aromatic aldehydes (0.01 mol) suspended in dry toluene was taken, and a presence of the catalytic amount of piperidine (0.5 ml) atreflux for 8–10 hours. The reaction contents were then poured into ice-cold water. The solid products (III) formed were filtered, washed, and dried. Finally, the products were re-crystallized from ethanol or methanol. The progress and completion of the reaction were confirmed by TLC to yield.

Table-1: Other Compounds of this III(a-n)) were Prepared by using the Same Method and their Physical Data were Recorded

S. No.	Compound Id	R	Molecular formula	M.W gm/ mole	M.P.	% Yield	Elemental Analysis					
							% of Carbon		% of Nitrogen		% of Hydrogen	
							%Cal	% Obt.	%Cal	% Obt.	%Cal	% Obt.
1.	III_a	-H	$C_{18}H_{14}N_2O_2$	290	282°C	75	74.47	74.58	9.65	9.75	4.86	4.87
2.	III_b	-3-NO_2	$C_{18}H_{13}N_3O_4$	335	265°C	65	64.47	64.58	12.53	12.55	3.91	3.94
3.	III_c	-4- Cl	$C_{18}H_{13}N_2O_2Cl$	325	235°C	70	66.57	66.58	8.63	8.95	4.03	4.04
4.	III_d	-4- OH	$C_{18}H_{14}N_2O_3$	306	262°C	64	70.58	70.55	9.15	9.25	4.61	4.64
5.	III_e	-2-OH	$C_{18}H_{14}N_2O_3$	306	250°C	73	70.58	70.56	9.15	9.27	4.61	4.65
6.	III_f	-4- OCH_3	$C_{19}H_{16}N_2O_3$	320	264°C	65	71.24	71.28	8.74	8.75	5.03	5.07
7.	III_g	-4-C_8H_7	$C_{20}H_{16}N_2O_2$	316	235°C	73	75.93	75.98	8.86	8.95	5.10	5.15
8.	III_h	-$N(CH_3)_2$	$C_{20}H_{19}N_3O_2$	333	255°C	65	72.05	72.08	8.00	8.05	5.74	5.78
9.	III_i	-3,4,-$(OCH_3)_2$	$C_{20}H_{16}N_2O_2$	376	239°C	78	68.56	68.58	12.60	12.68	5.18	5.20
10.	III_j	-2-Cl	$C_{18}H_{13}N_2O_2Cl$	325	268°C	56	66.57	66.58	8.63	8.65	4.03	4.05
11.	III_k	-2-NO_2	$C_{18}H_{13}N_3O_4$	335	248°C	74	64.47	64.58	12.53	12.55	3.91	3.93
12.	III_l	-3-OCH_3, 4–OH	$C_{19}H_{16}N_2O_4$	336	285°C	56	67.85	67.58	8.33	8.35	4.79	4.78
13.	III_m	2,4-$(OH)_2$	$C_{18}H_{14}N_2O_4$	322	265°C	68	67.07	67.18	8.69	8.65	4.38	4.39
14.	III_n	-5-Br	$C_{18}H_{13}N_2O_2Br$	369	255°C	78	58.56	58.58	7.59	7.75	3.55	3.57

Spectral Data of Synthesized Compounds

1-Benzoyl-4-benzylidene-3-methyl-1*H*-pyrazol-5(4*H*)-one (III_a)

FTIR: (cm^{-1}, KBr): 1665(C=O stretching, Pyrazole ring),1677(C=N stretching),1685(C=O stretching, amide), 2935(C-H stretching in CH_3), DMSO, 400 MHz,^{1}H NMR 2.5(3H, s, CH_3), 6.2(1H, s, CH), 6.5-

7.8(10H, m, aromatic ring), ^{13}C NMR: (DMSO, δ ppm): 111.11-124.45(Ar-C), 122.5(C=C), 142.8(C=N), 171.34(C=O), Elemental Analysis calculated: C-74.47%, H-4.86%, N-9.65%, Found: C-74.58%, H-4.87%, N-9.75%, MS(m/z): 290,Molecular formula: $C_{18}H_{14}N_2O_2$.

1-Benzoyl-4-(3-nitrobenzylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (III_b)
FTIR: (cm^{-1}, KBr): 1350(N=O stretching, aromatic NO_2), 1632(C=O stretching, pyrazolering),1667(C=N stretching), 1700(C=O stretching, amide), 2928(C-H stretching in CH_3), DMSO, 400MHz,
^{1}H NMR :3.3(3H, s, CH_3), 6.2(1H, s, CH), 6.8-7.9(9H, m, aromatic ring),
^{13}C NMR:(DMSO, δ ppm): 111.13-124.45(Ar-C), 120.5(C=C), 142.8(C=N), 171.44(C=O),
Elemental Analysis Calculated: C-64.47%, H-3.91%, N-12.53%, Found:C-64.58%, H-3.94%, N-12.55%, MS (m/z): 335,Molecular formula: $C_{18}H_3N_3O_4$.

1-Benzoyl-3-methyl-4-(4-chlorobenzylidene)-1*H*-pyrazol-5(4*H*)-one ($IIII_c$)
FTIR: (cm^{-1}, KBr): 706 (C-Cl stretching), 1632(C=O stretching pyrazole ring), 1667(C=N stretching), 1708(C=O stretching, amide), 2936(C-H stretching in CH_3),DMSO, 400 MHz,^{1}H NMR:2.8(3H, s, CH_3), 5.6(1H, s, CH), 7.1-7.9(9H, m, aromatic ring),^{13}C NMR: (DMSO, δ ppm): 111.11-129.49(Ar-C), 120.5(C=C), 142.8(C=N), 171.45(C=O), Elemental Analysis Calculated: C-66.57%, H-4.03%, N-8.63%, Found: C-66.58%, H-4.04%, N-8.95%,MS (m/z): 325,Molecular formula: $C_{18}H_{13}ClN_2O_2$.

1-Benzoyl--3-methyl-4-(4-hydroxybenzylidine)-1*H*-pyrazol-5(4*H*)-one (III_d)
FTIR: (cm^{-1}, KBr): 1635(C=O stretching), 1665(C=N stretching, pyrazole ring), 1685(C=OStretching, amide), 2955(C-H stretchingin CH_3), 3015(O-H stretching),DMSO, 400 MHz,^{1}H NMR: 2.3(3H, s, CH_3), 5.3(1H, s, OH), 6.2(1H, s, CH), 6.7-7.9(9H, m, aromatic ring),^{13}C 54.55(-OCH_3), 82.05(C-OH), 112.11-125.45(Ar-C), 121.5(C=C), 141.8(C=N),172.44(C=O),Elemental Analysis calculated:C-70.58%, H-4.61%, N-9.15%,Found: C 70.55%, H-4.64%, N-9.25%, MS (m/z): 306,Molecular formula: $C_{18}H_{14}N_2O_3$.

1-Benzoyl-3-methyl-4-(2-hydroxybenzylidene)-1*H*-pyrazol-5(4*H*)-one (III_e)
FTIR :(cm^{-1}, KBr): 1635(C=O stretching, pyrazole ring), 1665(C=N stretching,pyrazole ring), 1689(C=O stretching, amide), 2945(C-H stretching in CH_3), 3026(O-Hstretching).DMSO, 400 MHz ,^{1}H NMR:2.3(3H, s, CH_3), 5.1(1H, s, OH), 6.1(1H, s, CH), 6.6-7.9(9H, m, aromatic ring) ^{13}C NMR: (DMSO, δ ppm): 82.05(C-OH), 112.11-125.45(Ar-C), 121.5(C=C), 141.8(C=N), 172.44(C=O),Elemental Analysis calculated: C-70.58%,H-4.61%, N-9.15%,Found: C-70.56%,H-4.65%, N-9.27%. MS (m/z): 306,Molecular formula: $C_{18}H_{14}N_2O_3$.

1-Benzoyl-3-methyl -4-(4-methoxybenzylidene)-1*H*-pyrazol-5(4*H*)-one (III_f)
IR: (cm^{-1}, KBr): 1632(C=O stretching, pyrazole ring), 1668(C=N stretching), 1701(C=Ostretching, amide), 2837(-OCH_3), 2934(C-H stretching in CH_3),DMSO, 400 MHz ,^{1}H NMR2.2(3H, s, CH_3), 3.3(3H, s, OCH_3), 6.2(1H, s, CH), 6.5-7.9(9H, m, aromatic ring).^{13}CNMR:(DMSO, δ ppm): 115.11-127.45(Ar-C), 122.5(C=C), 142.8(C=N), 171.54(C=O, ElementalAnalysis Calculated: C-71.24%, H-5.03%, N-8.74%,Found: C-71.28%, H-5.07%,N-8.75%),MS(m/z): 320, Molecular formula: $C_{19}H_{16}N_2O_3$.

1-Benzoyl-(3-methyl-4-phenylbut-en-1-ylidene)-1*H*-pyrazole-5(4*H*)-one (III_g)
IR: (cm^{-1}, KBr): 1603(C=N stretching), 1703(C=O stretching, pyrazole ring), 1723(C=OStretching, amide), 2975(C-H stretching in CH_3),^{1}H NMR: (DMSO, 400 MHz) (δ ppm):3.1(3H,s, CH_3), 6.3(1H, s, CH), 6.7-7.9(10H, m, aromatic ring),^{13}CNMR: (DMSO, δ ppm)110.21-132.45(Ar-C), 127.5(C=C), 143.8(C=N), 172.44(C=O), Elemental AnalysisCalculated: C-75.93%, H-5.10%, N-8.86%,MS: (m/z): 316,Molecular formula: $C_{20}H_{16}N_2O_2$, Found: C-75.98%, H-5.15%,N-8.95%.

1-Benzoyl-3-methyl-4-(4-dimethylaminobenzylidene)-1*H*-pyrazol-5(4*H*)-one (III_h)
IR: (cm^{-1}, KBr): 1665(C=N stretching), 1678(C=O stretching, pyrazole ring), 1704(C=O stretching, amide), 2931(C-H stretching in CH_3),DMSO, 400 MHz,^{1}H NMR:2.4(6H, s, NCH_3), 3.2(3H, s, CH_3), 6.1(1H, s, CH), 6.5-7.9 (8H, m, aromatic ring),^{13}C NMR: (DMSO, δ ppm): 110.11-126.45(Ar-C),

123.5(C=C), 143.7(C=N), 171.54(C=O), Elemental Analysis Calculated: C-72.05%, H-5.74%, N-8.00%,Found: C-72.08%, H-5.78%, N-8.05%.
MS: (m/z): 333,Molecular formula: $C_{20}H_{19}N_3O_2$.

1-Benzoyl-3-methyl-4-(3,4-dimethoxybenzylidene)-1*H*-pyrazol-5(4*H*)-one (III_i)
IR: (cm^{-1}, KBr): 1663(C=N stretching), 1684(C=O stretching, pyrazole ring), 1702(C=O stretching, amide), 2831(-OCH_3 stretching), 2985(C-H stretching in CH_3).
DMSO, 400 MHz ,^{1}H NMR :2.2(3H, s, OCH_3), 3.1(3H, s, CH_3), 6.3(1H, s, CH), 6.5-7.9(9H, m, aromatic ring),^{13}CNMR: (DMSO, δ ppm):53.56(-OCH_3), 113.15-124.35(Ar-C), 125.5(C=C), 142.8(C=N), 171.44(C=O), Elemental Analysis Calculated: C-68.56%, H-5.18%, N-12.60%, Found: C-68.58%, H-5.20%, N-12.68%,MS (m/z): 376,
Molecular formula:$C_{20}H_{16}N_2O_2$.

1-Benzoyl-3-methyl-4-(2-chlorobenzylidene)-1*H*-pyrazol-5(4*H*)-one (III_j)
IR :(cm^{-1}, KBr): 745 (C-Cl stretching), 1665(C=N stretching), 1679(C=O stretching, pyrazole ring), 1704(C=O stretching, amide), 2955(C-H stretching in CH_3),DMSO, 400 MHz ,^{1}H NMR :2.2(3H, s, CH_3), 6.2(1H, s, CH), 6.4-7.9(9H, m, aromatic ring),^{13}C NMR (δ ppm, DMSO) 111.11-135.45(Ar-C), 120.5(C=C), 141.8(C=N), 172.44(C=O), , Elemental Analysis Calculated: C-66.57%, H-4.03%, N-8.63%, Found: C-66.58%, H-4.05%, N-8.65%,MS(m/z): 325, Molecular formula: $C_{18}H_{13}N_2O_2Cl$.

1-Benzoyl-3-methyl-4-(2-nitrobenzylidene)-1*H*-pyrazol-5(4*H*)-one (III_k)
IR: (cm^{-1}, KBr): 1535(N=O stretching, aromatic NO_2), 1632(C=O stretching, pyrazole ring), 1703(C=O stretching, amide), 1667(C=N stretching), 2929(C-H stretching in CH_3),DMSO, 400 MHz,^{1}H NMR:3.3(3H, s, CH_3), 6.1(1H, s, CH), 6.7-8.7(9H, m, aromatic ring),^{13}C NMR: (DMSO, δ ppm): 124.11-134.45(Ar-C), 144.5(C=C), 147.8(C=N), 148.65 (C-NO_2), 171.44 (C=O), Elemental Analysis Calculated: C-64.58%, H-3.93%, N-12.55%, Found: C-64.58%, H-3.93%, N-12.55%,MS(m/z): 335,
Molecular formula: $C_{18}H_3N_3O_4$

1-Benzoyl-3-methyl -4-(3-methoxy-4-hydroxybenzylidene)-1*H*-pyrazol-5(4*H*)-one (III_l)
IR: (cm^{-1}, KBr): 1667(C=N stretching), 1654(C=O stretching, pyrazole ring), 1703(C=O stretching, amide), 2820(-OCH_3), 2956(C-H stretching in CH_3), 3066(O-H stretching).
DMSO, 400 MHz ,^{1}H NMR :2.3(3H, s, OCH_3), 3.3(3H, s, CH_3), 5.1(1H, s, OH), 6.1(1H, s, CH), 6.3-7.9 (8H, m, aromatic ring).^{13}C NMR: (DMSO, δppm): 54.65(-OCH_3), 82.15(C-OH), 111.11-126.45(Ar-C), 121.5(C=C), 141.8(C=N), 172.44(C=O), Elemental Analysis Calculated: C-67.85%, H-4.79%, N-8.33%,Found: C-67.58%, H-4.78%, N-8.35%,MS(m/z): 336,Molecular formula: $C_{19}H_{16}N_2O_4$.

1-Benzoyl-3-methyl-4-(2,4-dihydroxybenzylidene)-1*H*-pyrazol-5(4*H*)-one (III_m)
FTIR: (cm^{-1}, KBr): 1665(C=N stretching), 1678(C=O stretching pyrazole ring), 1706(C=O stretching, amide), 2925(C-H stretching in CH_3), 3036(-O-H stretching), DMSO, 400 MHz ,^{1}H NMR,2.4(3H, s, CH_3), 5.2(2H, s), 6.3(1H, s, CH), 6.3-7.9(8H, m, aromatic ring).
^{13}C NMR: (DMSO, δppm): 81.05(C-OH), 113.11-128.45(Ar-C), 121.5(C=C), 142.8(C=N), 173.44(C=O), Elemental Analysis Calculated: C-67.07%, H-4.38%, N-8.69%,
Found: C-67.18%, H-4.39%, N-8.65%,MS(m/z): 322,Molecular formula: $C_{18}H_{14}N_2O_4$.

1-Benzoyl-3-methyl 4-(5-bromobenzylidene)-1*H*-pyrazol-5(4*H*)-one (III_n)
IR: (cm^{-1}, KBr): 565(C-Br stretching), 1667(C=N stretching), 1689(C=O stretching, pyrazole ring), 1705(C=O stretching, amide), 2915(C-H stretching in CH_3),DMSO, 400 MHz ,^{1}H NMR:2.4(3H, s, CH_3), 6.3(1H, s, CH), 6.5-7.9(9H, m, aromatic ring),^{13}CNMR: (DMSO, δppm):113.11-125.45(Ar-C), 122.5(C=C), 142.8(C=N), 173.44(C=O), Elemental Analysis alculated: C-58.56%, H-3.55%, N-7.59%,
Found: C-58.58%, H-3.57%, N-7.75%. MS(m/z): 369, Molecular formula: $C_{18}H_{13}N_2O_2Br$.

RESULTS AND DISCUSSION

In the present work, we have prepared a new series of pyrazole derivatives. The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR, and mass spectral analysis.Compound III_a showed strong stretching at 1665 cm^{-1} due to the carbonyl group. Compound **I**II_i showed strong

stretching at 1702cm^{-1} due to the carbonyl group and C=N stretching at 1663cm^{-1}. All the synthesized compounds were screened for antibacterial and antifungal activities by broth dilution method. From the study of the biological activity data in reference to the standard drugs ampicillin and Amphotericin B, we found that compound III_lexhibited good activity against *S. aureus*, and compounds III_c, III_a, III_m, and III_k gave moderate activity against *S. aureus*.

CONCLUSION

In the present study, it was observed that the pyrazole moiety can be considered a promising pharmacophore for better antibacterial activities. It was found that varying the substitution in the final structure affected the biological activities. Final compounds with chloro, hydroxy, nitro, and methoxy were found to possess moderate antibacterial activity, and some of the compounds, for example, III_g, III_j, III_n moderate activity against *Aspergilliusniger*.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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REFERENCES

1. T. Eicher, S. Hauptmann, A. Speicher, *Wiley-VCH,* **1,** (2003), https://doi.org/10.1002/352760183X
2. E. V. Pimerova, E. V. Voronina, *Pharmceutical Chemistry Journal*, **35(11),** 602(2001), http://dx.doi.org/10.1023/A:1015141710100
3. H. J. Park, L. Lee, S. Park, B. Ahn, J. C. Lee, H. Y. Cho, K. i. Lee, *Bioorganic and medicinal Chemistry Letters*, **15(13),** 3307(2005), https://doi.org/10.1016/j.bmcl.2005.03.082
4. D. M. Bailey, P. E. Hansen, A. G. Hlavac, E. R. Baizman, J. Pearl, A. F. Defelice, M. A. Feigenson, *Journal of Medicinal Chemistry*, **28(2),** 256(1985), https://doi.org/10.1021/jm00380a020
5. T. I. EL-Emary, A. Khalil, G. A. M. EL-hag Ali and A. A. A. M. EL-adasy, *Phosphorus, Sulfur, and Silicon and the Related Elements,* **180(1),** 19(2005), https://doi.org/10.1080/10426500490494778
6. E. Akbas, I. Berber, A. Sener and B. hasanvov, *Elsevier Masson. IL Farmaco,* **60 (1),** 23(2005), https://doi.org/10.1016/j.farmac.2004.09.003
7. A. Tanitame, Y. Oyamada, K. Ofuji, H. Tearauchi, M. Kawasaki, M. Wachi and J. Yamagishi, *Bioorganic & Medicinal Chemistry*, **12 (21),** 5515(2004), https://doi.org/10.1016/j.bmc.2004.08.010
8. T. I. El-Emary, A. M. Kamal EL-Dean and H. S. El-kashef, *IL Farmaco,* **53(6),** 383(1998), https://doi.org/10.1016/S0014-827X(98)00014-7
9. J. Sun, Y. Zhou, *Molecules,* **20(3),** 4383(2015), https://doi.org/10.3390/molecules20034383
10. V. Rastija, K. Vrandecic, J. Cosic, K. S. Gabriella, I. Majic, D. Agic, D. Subaric, M. Karnas, D. Beslo, H. Brahmbha, M. Komar, *International Journal of Molecular Science*, **24(11),** 9335(2023). https://doi.org/10.3390/ijms24119335

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