REVIEW OF RESEARCH
IMPACT FACTOR : 5.7631(UIF) UGC APPROVED JOURNAL NO. 48514 ISSN: 2249-894X
VOLUME - 8 | ISSUE - 5 | FEBRUARY - 2019

ASYMMETRICAL PYRAZOLE CURCUMIN ANALOGUES: POTENTIAL ANTIOXIDANT AGENTS

Shravan Y. Jadhav[1], Nargisbano A. Peerzade[2] and Raghunath B. Bhosale[2]
[1]Department of Chemistry, D.B.F. Dayanand College of Arts & science, Solapur, Maharashtra, India.
[2]Organic Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur, Maharashtra, India.

ABSTRACT :

The new series of asymmetrical pyrazole curcumin analogues 4a-f were synthesized by using polyethylene glycol (PEG-400) as a green reaction medium and evaluated for their in vitro antioxidant activity. All the synthesized compounds were characterized by using IR, 1H NMR, LC-MS spectroscopic methods. Among the synthesized compounds, compounds 4f, 4a, 4b and 4d were found to be most active hydrogen peroxide scavengers as compared to the standard butylated hydroxytoluene (BHT).

KEYWORDS : *Asymmetrical Pyrazole Curcumin, PEG-400, Antioxidant activity.*

INTRODUCTION :

Curcumin has a wide range of interesting biological activities such as anti-inflammatory, antioxidant, antiviral, cutaneous wound healing, hypocholesterolemic effects in diabetic patients, anti-angiogenic and stimulatory response to stress-induced biological activity.[1,2] Curcumin has been demonstrated to possess preventative activity against Aβ-aggregation in Alzheimer's model.[3]

Presently, curcumin has been evaluated in clinical trials for the treatment of many diseases such as liver disease, rheumatoid arthritis, infectious diseases and various cancers, including leukemia, colon, liver, breast and prostate cancers.[4-6] The therapeutic effects of curcumin are attributed to its activity on a wide range of molecular targets, particularly a series of inflammatory factors and cytokines. Extensive literature survey and clinical reports suggests that curcumin has potential in prevention and treatment of variety of other diseases.

Oxidative stress and oxidative damage are involved in the pathophysiology of many chronic inflammatory and degenerative disorders, particularly such as cancer. The generation of ROS, particularly O_2^- and $OH^{\cdot}$, play important roles in the development of cancer.[7,8] Therefore in order to prevent from the oxidative damage of DNA, lipid or protein the effects of these free radicals can be diluted by the anti-oxidant mechanism.

In vitro, curcumin can significantly inhibit the generation of reactive oxygen species (ROS) like superoxide anions, H_2O_2 and nitrite radical generation by activated macrophages, which play an important role in inflammation. It lowers the production of ROS *in vivo.*[9] Curcumin exerts powerful inhibitory effect against H_2O_2-induced damage in human keratinocytes and fibroblasts and in NG 108-15 cells.[10] Curcumin reduces oxidized proteins in amyloid pathology in Alzheimer transgenic mice.[11] It also decreases lipid peroxidation in rat liver microsomes, erythrocyte membranes and brain homogenates. This is brought about by maintaining the activities of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase.[12] Since ROS have been implicated in the development of various pathological conditions,[13-15] curcumin has the potential to control these diseases through its potent antioxidant activity.

Contradictory to the above-mentioned antioxidant effect, curcumin has pro-oxidant activity. Kelly *et al.,*[16] reported that curcumin not only failed to prevent single-strand DNA breaks by H_2O_2, but also caused DNA damage. As this damage was prevented by antioxidant *α*-tocopherol, the pro-oxidant role of curcumin has been proved. Curcumin also causes oxidative damage of rat hepatocytes by oxidizing glutathione and of human erythrocyte by oxidizing oxyhaemoglobin, thereby causing haemolysis.[17] The prooxidant activity appears to be mediated through generation of phenoxyl radical of curcumin by peroxidase–H_2O_2 system, which cooxidizes cellular glutathione or NADH, accompanied by O_2 uptake to form ROS.[17] The antioxidant mechanism of curcumin is attributed to its unique conjugated structure, which includes two methoxylated phenols and an enol form of *β*-diketone; the structure shows typical radical-trapping ability as a chain-breaking antioxidant. [18,19]

With our recent success on the development of new selective eco-friendly methodologies using polyethylene glycol (PEG-400) (20, 21) as a green solvent for the preparation of biologically active compounds, herein we report the synthesis of some new series of asymmetrical pyrazole curcumin analogues (APCAs) using aq.NaOH in PEG-400 as green alternative reaction medium and evaluate as analgesic agent along with assessing their antioxidant potential.

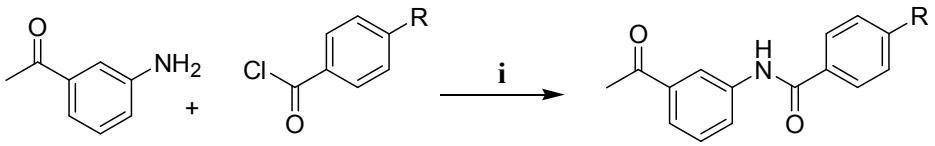
METHODS AND MATERIALS

Instrumentation

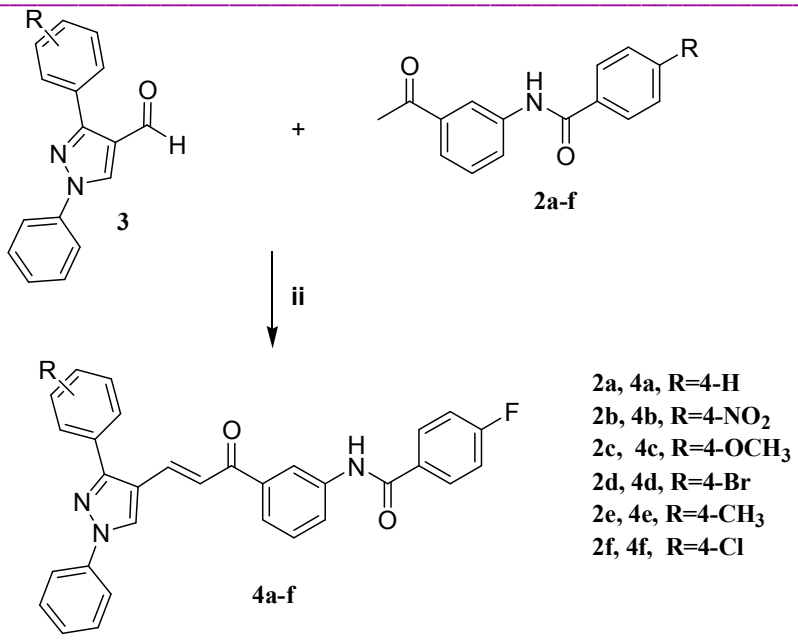
Melting points were determined in open capillary tubes and were found uncorrected. IR spectra were recorded on FT-IR spectrometer(Perkin Elmer) using KBr disc method.^{1}HNMR spectra were recorded on ^{1}HNMR (Varian-NMR-mercury 300 MHz) spectrometer in $CDCl_3$ as solvent. All chemical shifts (δ) are quoted in parts per million downfield from TMS and coupling constants (J) are given in hertz. Abbreviations used in the splitting pattern were as follows: s = singlet, d = doublet, t= triplet, q = quintet, m = multiplet. The mass spectra were obtained with a Shimadzu LCMS-2010 EV. All the reagents and solvents used were of analytical grade and were used as supplied unless otherwise stated. TLC was performed on silica gel coated plates for monitoring the reactions.

Chemistry

The asymmetrical pyrazole curcumin analogues (APCAs) are prepared by straight forward chemistry. Acylation of 3-aminoacetophenone (**1**) with substituted acyl chloride to afford corresponding substituted amides (**2a-f**), which on Claisen-Schmidt condensation with Fluoro substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**3)** and NaOH in PEG-400 furnished APCAs (**4a-f)** in good to excellent yields (**Scheme-1**). The completion of the reaction was monitored by TLC. The Fluoro substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**3**) were prepared by the Vilsmeir-Haack reaction (22) of fluoro substituted aryl hydrazones from fluoro substituted acetophenone. All the synthesized compounds were characterized by IR, ^{1}HNMR and Mass spectroscopy.



1 **2a-f**



Scheme1. Reagents and conditions: (**i**) NaOH, 70-80°C, 30 min.
(**ii**) NaOH, PEG-400, stirr, 40-50 °C, 1 h.

General procedure for the preparation substituted-benzamide compounds (2a-f)

1-(3-Amino-phenyl) ethanone **1** (1 g, 7.40 mM) was suspended in 20 mL of 5 % of sodium hydroxide solution in a well-corked two necked round bottom flask and added 2 mL of various substituted benzoyl chloride, 0.5 mL at a time, with constant shaking and stirred vigorously for 10 min, reaction mixture was heated under reflux on water bath at 70-80 °C for 30 min until the odor of the benzoyl chloride was disappeared. Make sure that the mixture has an alkaline pH. Filter off the solid benzoyl derivative and recrystallized it from petroleum ether and ethyl acetate to obtain compound **2a-f**.

General procedure for the preparation of asymmetrical pyrazole curcumin analogues (4a-g)

The Fluoro substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **3** was prepared by Vilsmeier-Haack reaction on acetophenone hydrazones obtained from fluoro substituted acetophenone according to literature method (22). A mixture of Fluoro substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **3** (1 mM) and ***substituted-benzamide compounds*** **2a-f** (1 mM) was dissolved in 15 mL PEG-400. To this mixture, NaOH (20%, 1mL) was added and the reaction mixture was stirred at 40-50°C temperature for 1h. The reaction mixture was then poured into 100 mL ice cold water. The product was separated out; it was filtered and processed out. The products obtained were recrystallized from ethanol to afford pure compounds **4a-g**.

Hydrogen Peroxide (H_2O_2) Scavenging activity:

The hydrogen peroxide scavenging assay was performed by the reported method (23). A solution of hydrogen peroxide (40 mM) was prepared in phosphate buffer (pH 7.4). The 1 mM concentrations of various compounds were added to a hydrogen peroxide solution (0.6 mL, 40 mM). Absorbance of hydrogen peroxide at 230 nm was determined after 10 min. against a blank solution containing phosphate buffer without drug. The percentage scavenging of hydrogen peroxide of synthetic compounds and standard compounds was calculated using the following formula:

% scavenged $[H_2O_2] = [(A_0-A_1)/A_0] \times 100$

Where,

A_0 = the absorbance of the control

A_1 = the absorbance in the presence of the sample of MO and standards.

RESULTS AND DISCUSSION

Spectral analysis

All the synthesized compounds were characterized by IR, ^{1}H NMR, and MS. The IR spectrum of the titled compounds showed absorption due to –NH stretching at ~3350 cm-1, amide carbonyl group at ~1645 cm-1. ^{1}H NMR spectrum (300 and 400 MHz) recorded in DMSO-d6 showed a typical singlet at δ ~ 9-10 (for -NH) and a typical 1H-1H coupling constant in between 12-16 Hz showing *trans* stereochemistry of the double bond.

N-(3-acetyl-phenyl)-benzamide (2a)

MF/FWt: $C_{15}H_{13}NO_2$ / 239, **Yield**: 67 %, **MP**: 80-82^{o}C, **IR** (KBr, cm-1): 3444, 3296, 3200, 3037, 2968, 1712, 1699, 1615, 1493, 1377, 1267, 1203, 1061, 842 cm^{-1}; **1H NMR** (300 MHz, CDCl3, δ in ppm): 8.39 (broad s, 1H); 8.182 (s, 1H); 8.09 (dd, 1H, *J* =2.0 Hz); 7.91 (d, 2H, *J* = 8.0 Hz); 7.71 (d, 1H, *J* = 8.0 Hz); 7.55 (t, 1H, *J* = 8.0 Hz); 7.473 (m,3H); 2.53 (s, 3H); **MS**: m/e = 240 (M+1).

N-(3-{3-[3-(4-fluoro-phenyl)-1-phenyl-1H-pyrazol-yl]-acryloyl}-phenyl)-benzamide (4a)

MF/FWt: $C_{31}H_{22}N_3O_2F$ / 487, **Yield:** 82 %, **MP:** 242-244 ^{o}C, **IR** (KBr): 3278, 3067, 2917, 2849, 1660, 1646, 1596, 1584, 1541, 1483, 1226, 843, 756 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.39-8.43 (m, 18H, Ar-H); 7.42 (d, 1H, *J* = 16.0 Hz, -CH=CH-); 7.97 (d, 1H, *J* = 16.0 Hz, -CH=CH-); 9.4 (s, 1H, pyrazole-H); 10.5 (s, 1H, N-H, D_2O exchangeable).

N-(3-acetyl-phenyl)-4-nitro-benzamide (2b)

MF/FWt: $C_{15}H_{12}N_2O_4$ / 284, **Yield:** 65 %, **MP:** 238-240 ^{o}C, **IR** (KBr): 3418, 3298, 3219, 3088, 2950, 1690, 1638, 1599, 1498, 1385, 1288, 1206, 1131, 1076, 867, 766 cm^{-1}; **^{1}H NMR** (300 MHz, CDCl3, δ in ppm): 8.15 (broad s, 1H); 8.09 (d, 2H, *J* = 8 Hz); 7.89 (s, 1H); 7.77 (d, 2H, *J* = 8 Hz); 7.48 (m, 2H); 7.39 (m, 1H); 3.96 (s, 3H); **MS:** m/e 285 (M+1).

N-(3-{3-[3-(4-fluoro-phenyl)-1-phenyl-1H-pyrazol-yl]-acryloyl}-phenyl)-4-nitro-benzamide (4b)

MF/FWt: $C_{31}H_{21}N_4O_4F$ / 532, **Yield:** 78 %, **MP:** 240^{o}C, **IR** (KBr): , 3290, 3180, 2930, 2824, 1640, 1650, 1592, 1526, 1500, 1409, 1222, 844, 753 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.18-8.41 (m, 17H, Ar-H); 7.39-7.43 (d, 1H, *J* = 16.0 Hz, -CH=CH-); 7.83-7.87 (d, 1H, *J*=15.0 Hz, -CH=CH-); 9.42 (s, 1H, pyrazole-H); 10.54 (s, 1H, N-H, D_2O exchangeable).

MS: m/e 533 (M+1).

N-(3-acetyl-phenyl)-4-methoxy-benzamide (2c)

MF/FWt: $C_{16}H_{15}NO_3$ / 269, **Yield:** 73 %, **MP:** 97-99 ^{o}C, **IR** (KBr): 3415, 3293, 3213, 3082, 2950, 1690, 1628, 1599, 1495, 1382, 1285, 1206, 1131, 1074, 863, 766 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, δ in ppm): 8.14 (broad s, 1H); 8.06 (d, 2H, *J* = 8 Hz); 7.88 (s, 1H); 7.74 (d, 2H, *J* = 8 Hz); 7.47 (m, 2H); 7.37 (m, 1H); 3.95 (s, 3H); 2.56 (s, 3H); **MS:** m/e 270 (M+1).

N-(3-{3-[3-(4-fluoro-phenyl)-1-phenyl-1*H*-pyrazol-yl]-acryloyl}-phenyl)-4-methoxy-benzamide (4c)

MF/FWt: $C_{32}H_{24}N_3O_3F$ / 517, **Yield:** 85 %, **MP:** 224^{o}C, **IR** (KBr): 3292, 3122, 3061, 2841, 1663, 1642, 1607, 1527, 1505, 1485, 1246, 844, 751 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ 3.85 (s, 3H, OCH_3); 7.41-8.41 (m, 18H, Ar-H); 7.56-7.60 (d, 1H, *J* = 16.0 Hz, -CH=CH-); 7.95-7.99 (d, 1H, *J* = 16.0 Hz, -CH=CH-); 9.45 (s, 1H, pyrazole-H); 10.34 (s, 1H, N-H, D_2O exchangeable); **MS:** m/e 518 (M+1).

Synthesis of N-(3-acetyl-phenyl)-4-bromo-benzamide (2d)

MF/FWt: $C_{15}H_{12}BrNO_2$ / 318., **Yield:** 71 %, **MP:** 167°C, **IR** (KBr) : 3450, 3410, 2940, 1698, 1635, 1501, 1377, 1281, 1210, 1069, 860 cm $^{-1}$; **^{1}H NMR** (300 MHz, $CDCl_3$, δ in ppm): 8.21 (broad s, 1H); 8.16 (m, 1H); 8.01 (d, 1H, *J* = 8 Hz); 7.89 (m, 1H); 7.75 (m, 2H); 7.50 (m, 3H); 2.61 (m, 3H); **MS:** m/e 319 (M+1).

4-bromo-N-(3-{3-[3-(4-fluoro-phenyl)-1-phenyl-1*H*-pyrazol-yl]-acryloyl}-phenyl)-benzamide (4d)

MF/FWt: $C_{31}H_{21}N_3O_2FBr$ / 566, **Yield:** 82%, **MP:** 256°C, **IR** (KBr): 3271, 3123, 2917, 2849, 1663, 1642, 1606, 1594, 1529, 1483, 1246, 844, 751 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.41-8.40 (m, 17H, Ar-H); 7.58-7.62 (d, 1H, *J* = 16.0 Hz, -CH=CH-); 7.94-8.00 (d, 1H, *J* = 16.0 Hz, -CH=CH-); 9.45 (s, 1H, pyrazole-H); 10.56 (s, 1H, N-H, D_2O exchangeable); **MS:** m/e 568 (M+2).

N-(3-acetyl-phenyl)-4-methyl-benzamide (2e)

MF/FWt: $C_{16}H_{15}NO_2$ / 253, **Yield**: 55 %, **MP**: 135-137°C, **IR** (KBr, cm-1): 3412, 3290, 3212, 3071, 2948, 1693, 1628, 1596, 1493, 1384, 1281, 1203,1120, 1075, 868, 752 cm^{-1}; **1H NMR** (300 MHz, CDCl3, δ in ppm): 8.12 (broad s, 1H); 8.05 (d, 1H,*J*= 7.6 Hz); 7.90 (s,1H); 7.72 (d, 1H, *J* = 7.6 Hz); 7.48 (m, 2H); 7.37 (m, 1H); 7.26 (m, 2H); 2.56 (s, 3H); 2.40 (s,3H); **MS**: m/e = 254 (M+1).

N-(3-{3-[3-(4-fluoro-phenyl)-1-phenyl-1*H*-pyrazol-yl]-acryloyl}-phenyl)-4-methyl-benzamide (4e) \

MF/FWt: $C_{32}H_{24}N_3O_2F$ / 501, **Yield:** 86 % **MP:** 232°C, **IR** (KBr): 3279, 3122, 3062, 2853, 1662, 1645, 1607, 1533, 1505, 1485, 1246, 844, 752 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 2.50 (s, 3H, CH_3), 7.35-8.42 (m, 17H, Ar-H); 7.58-7.62 (d, 1H, *J = 16*.0 Hz, -CH=CH-); 7.91-7.95 (d, 1H, *J = 16*.0 Hz, -CH=CH-); 9.45 (s, 1H, pyrazole-H); 10.41 (s, 1H, N-H, D_2O exchangeable); **MS:** m/e 502 (M+1).

N-(3-acetyl-phenyl)-4-chloro-benzamide (2f)

MF/FWt: $C_{15}H_{12}ClNO_2$ / 273, **Yield**: 60 %, **MP**: 144-146°C, **IR** (KBr, cm-1): 3444, 3296, 3077, 2968, 1712, 1699, 1615, 1493, 1377, 1267, 1061, 842 cm^{-1}; **1H NMR** (300 MHz, CDCl3, δ in ppm): 8.22 (broad s, 1H); 8.13 (s, 1H); 8.04 (d, 2H, *J*= 8Hz); 7.88 (m, 1H); 7.72 (d, 2H, *J* = 8 Hz); 7.42 (m, 2H); 2.31 (s, 3H) **MS**: m/e = 274 (M+1).

4-chloro-N-(3-{3-[3-(4-fluoro-phenyl)-1-phenyl-1*H*-pyrazol-yl]-acryloyl}-phenyl)-benzamide (4f)

Yield: 75%, **MF/FWt:** $C_{31}H_{21}N_3O_2ClF$ / 521, **MP:** 246°C, **IR**(KBr): 3273, 3126, 3070, 2917, 2848, 1664, 1642, 1606, 1594, 1536, 1485, 1246, 840, 753 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): 7.41-8.40 (m, 17H, Ar-H); 7.58-7.62 (d, 1H, *J* = 16.0 Hz, -CH=CH-); 8.04-8.08 (d, 1H, *J* = 16.0 Hz, -CH=CH-); 9.45 (s, 1H, pyrazole-H); 10.56 (s, 1H, N-H, D_2O exchangeable); **MS:** m/e 522 (M+1).

Biological studies

In vitro antioxidant activity

All the compounds synthesized (APCAs) were evaluated for their direct scavenging activity against reactive oxygen species such as hydrogen peroxide and results are presented in **Table 1**.

Table 1. Antioxidant (hydrogen peroxide scavenging) activity of compounds 4a-g.

Sr. No.	Entry	Antioxidant activity H_2O_2 (%)
1.	4a	81.48
2.	4b	68.68
3.	4c	21.35
4.	4d	48.17
5.	4e	18.29.

6.	4f	82.06
Stan dard	BHT	88.42

BHT – butylated hydroxytoluene;

All the synthesized compounds have shown good to moderate scavenging activity against hydrogen peroxide. The antioxidant activity result reveals that the compounds **4f** (82.06%), 4a (81.48) were found to possess excellent inhibition of H_2O_2 scavenging activity followed by compound **4b** (68.68%) as compared to the BHT (88.42%). The compound **4d** (48.17%) showed moderate activity whereas remaining compounds **4c**, and **4e** showed weak inhibition of H_2O_2 scavenging activity. The wide variation in the free radical scavenging potential for the tested compounds may be due to the variation in the proton–electron transfer by the derivatives due to difference in their structures.

CONCLUSION

In conclusion, a series of new asymmetrical pyrazole curcumin analogues (APCAs) (**4a-f**) have been synthesized by using PEG-400 as a alternative reaction medium and were characterized by IR, ^{1}H NMR and mass spectrometry. The reaction was clean and the products were obtained in excellent yields without formation of any detectable side products. All the newly synthesized compounds (**4a-f**) were evaluated for antioxidant potential. The SAR study reveals that compounds with electron withdrawing groups (**4f, 4b** and **4d)** or without electron withdrawing group (**4a**) showed excellent inhibition of H_2O_2 scavenging activity, whereas compounds containing electron donating groups (**4c** and **4e**) showed weak inhibition of H_2O_2 scavenging activity as compared to standard. Thus, these compounds constitute an interesting template for the evaluation of new antioxidant agents and may be helpful for the design of new therapeutic tools.

ACKNOWLEDGMENTS

Author is thankful to P. A. H. Solapur University, Solapur for granting Minor Research Project under the “Seed Money for Research” scheme (Reference: SUS/TA-2/2017-18/3901 dated 8th May 2018). Author also thankful to The Principal, D.B.F Dayanand College of Arts and Science, Solapur for their constant encouragement and guidance.

Conflict of Interest

Authors have no conflict of interest.

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