Bioorganic & Medicinal Chemistry Letters 23 (2013) 2575–2578

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

PEG mediated synthesis and pharmacological evaluation of some fluoro substituted pyrazoline derivatives as antiinflammatory and analgesic agents

Shravan Y. Jadhav [a], Sachin P. Shirame [a], Suresh D. Kulkarni [b], Sandeep B. Patil [c], Sharad K. Pasale [d], Raghunath B. Bhosale [a,*]

[a] Organic Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur 413255, Maharashtra, India
[b] Pharmacology Department, Luqman College of Pharmacy, Gulberga 584102, Karnataka, India
[c] Pharmacology Department, Appasaheb Birnale College of Pharmacy, Sangli 416416, Maharashtra, India
[d] Department of Chemical Science, University of 'Tor Vergata', Rome, Italy

ARTICLE INFO

Article history:
Received 18 December 2012
Revised 8 February 2013
Accepted 26 February 2013
Available online 7 March 2013

Keywords:
Pyrazolines
PEG-400
Antiinflammatory activity
Analgesic activity

ABSTRACT

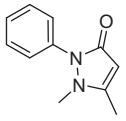
A new series of fluoro substituted pyrazoline derivatives **5a–g** and **6a–g** were synthesized in good to excellent yield from the corresponding pyrazole chalcones, **4a–g**, by using polyethylene glycol-400 (PEG-400) as an alternative reaction medium. The newly synthesized compounds were characterized and screened for their in vivo antiinflammatory and analgesic activity. Compounds **5g** and **6g** were found to be more potent than standard drug Diclofenac and six other compounds **5b**, **5c**, **5f**, **6b**, **6c** and **6f** showed significant antiinflammatory activity as compared to standard drug. Compounds **5c**, **5d**, **5e**, **5f**, **6c**, **6d**, **6e** and **6f** showed significant analgesic activity as compared to standard drug Aspirin.

© 2013 Elsevier Ltd. All rights reserved.

Presently, the researchers have focused their interest in developing the alternative synthesis as well as insertion of a fluorine atom into the heterocyclic compounds in order to enhance the significant effect on the biological and physical parameters.[1] As the fluorinated compounds possess various biological activities which is due to their lipophilicity and stability,[2] the chemistry and pharmacology of these compounds is of great interest in the medicinal chemistry.

Pyrazoles are the most important class of heterocyclic compounds having their broad spectrum of application in pharmaceutical and agrochemical field.[3] Pyrazole derivatives are found to exhibit good antibacterial,[4] antiinflammatory,[5] analgesic,[6] anticancer, radio protective,[7] anti-convulsant[8] and anti-depressant activity.[9] Pyrazolines are well known nitrogen containing five-membered compounds which are found to possess considerable biological activities in the medicinal chemistry.[10–13]

The survey of literature reveals that many pyrazoline derivatives have been used for clinical application as NSAIDS. Phenylbutazone, Celecoxib and Deracoxib are the pyrazoline NSAIDS, are potent antiinflammatory and analgesic agents. Antipyrine is the first pyrazoline derivative used as an antipyrine agent. However their use is restricted due to their GI side effects. The development of alternatives to NSAIDs is being attempted all over the world.

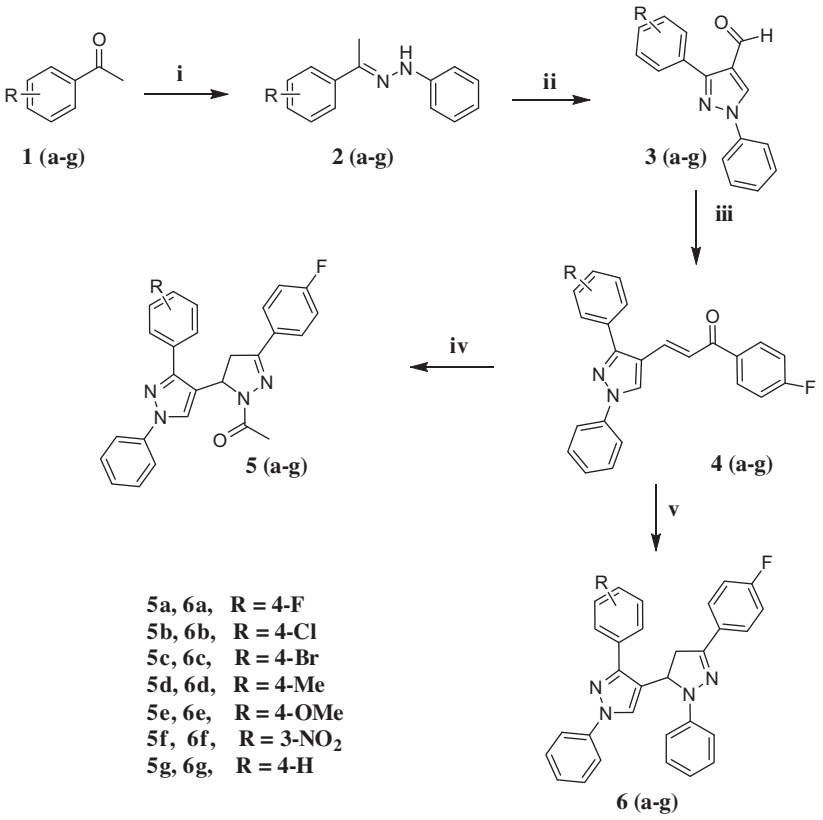


(a) Antipyrine

N-substituted pyrazoline derivatives also exhibit biological activities like COX-2 inhibitors,[14] antiinflammatory, analgesic, antimicrobial,[15,16] antitumor,[17] antileukemia,[18] anti-depressant,[19] angiotension converting enzyme inhibitory activity and hypertension.[20] The *N*-phenyl-3-(4-fluorophenyl)-4-substituted pyrazole derivatives are recently reported as antitubercular agents.[21,22] On the other hand, PEG solvents are known to be inexpensive, easily available, thermally stable, recyclable, biological compatible, non-toxic and water soluble compounds that does not hydrolyze on long storage.[23–25] Due to these advantages, PEGs of different molecular weights are extensively used as solvents or vehicles in various pharmaceutical industries. However, PEG polymer of low molecular weight differ significantly from polymers of high molecular weight in their physico-chemical properties, higher toxicity and possibly genotoxicity.[26] The toxicity data of different

* Corresponding author. Tel./fax: +91 217 2744770.
E-mail address: bhosale62@yahoo.com (R.B. Bhosale).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.02.105



Scheme 1. Reagents and conditions: (i) Phenyl hydrazine, methanol, concd H_2SO_4 (2 drops), 70 °C, 4 h. (ii) DMF, $POCl_3$, 80 °C, 5 h. (iii) 4-Fluoro acetophenone, NaOH, PEG-400, 40–50 °C, 1 h. (iv) $N_2H_4{\cdot}H_2O$, acetic acid, PEG-400, 70–75 °C, 4–5 h. (v) Phenyl hydrazine, NaOH, PEG-400, 70–75 °C, 4–5 h.

Table 1
Antiinflammatory activity of pyrazoline derivatives (**5a–g** and **6a–g**) by carrageenan induced rat paw edema method in rats and analgesic activity by tail flick method

Entry	Antiinflammatory activity Mean paw volume (mL) ± SEM				Analgesic activity % inhibition
	0 h	1 h	2 h	3 h	60 min
Control	1.25 ± 0.01	1.29 ± 0.01	1.32 ± 0.001	1.38 ± 0.001	—
Diclofenac	0.85 ± 0.02	0.66 ± 0.02	064 ± 0.001	0.58 ± 0.01	—
Aspirin	—	—	—	—	119
5a	1.25 ± 0.03	1.20 ± 0.04	1.37 ± 0.003	1.09 ± 0.004	43
5b	0.88 ± 0.01***	0.84 ± 0.04**	0.68 ± 0.001***	0.98 ± 0.002**	44
5c	0.76 ± 0.04**	0.88 ± 0.04**	0.66 ± 0.005**	0.68 ± 0.001**	71
5d	1.16 ± 0.05	1.39 ± 0.06	1.32 ± 0.004	1.26 ± 0.006	110
5e	1.36 ± 0.04	1.36 ± 0.01	1.48 ± 0.006	1.47 ± 0.003	66
5f	0.87 ± 0.05***	0.89 ± 0.04**	0.86 ± 0.006**	0.69 ± 0.005**	109
5g	0.57 ± 0.05***	0.58 ± 0.05***	0.38 ± 0.003***	0.59 ± 0.003***	35
6a	1.15 ± 0.03	1.19 ± 0.04	1.36 ± 0.003	1.08 ± 0.004	41
6b	0.78 ± 0.01***	0.77 ± 0.04**	0.64 ± 0.001***	0.96 ± 0.002**	43
6c	0.76 ± 0.02**	0.87 ± 0.04**	0.69 ± 0.005**	0.68 ± 0.001**	71
6d	1.15 ± 0.02	1.29 ± 0.06	1.32 ± 0.005	1.26 ± 0.006	110
6e	1.35 ± 0.01	1.30 ± 0.01	1.42 ± 0.006	1.48 ± 0.003	66
6f	0.86 ± 0.02***	0.79 ± 0.05**	0.84 ± 0.006**	0.69 ± 0.005**	108
6g	0.58 ± 0.01***	0.59 ± 0.04***	0.38 ± 0.003***	0.59 ± 0.003***	35

SEM—standard error mean; $n = 6$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; —, not determined.

molecular weight PEG's are also available and some of them are already approved for internal consumption by the USA FDA.[27] The use of PEG as a green and alternative reaction medium in organic reactions is relatively recent.[28]

Appreciation of these findings motivated us to synthesize some new fluoro substituted pyrazoline derivatives by using polyethylene glycol (PEG-400) as an alternative reaction medium which have been found to possess an interesting profile for antiinflammatory and analgesic activity.

The synthesis of pyrazoline derivatives were prepared as outlined in Scheme 1. The substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehydes **3a–g** were prepared by Vilsmeier–Haack reaction on acetophenone hydrazones **2** obtained from various substituted acetophenones **1** according to literature method.[29] The pyrazole chalcones **4a–g** were prepared by the reaction of various substituted pyrazole aldehydes **3a–g** with 4-fluoroacetophenone and NaOH in PEG-400. These pyrazole chalcones **4a–g** were treated with hydrazine hydrate/acetic acid and phenyl hydrazine/NaOH

in PEG-400 and heated for about 4–5 h to afford pyrazoline derivatives **5a–g** and **6a–g** respectively. The completion of the reaction was monitored by TLC. All the synthesized compounds were characterized by IR, ^{1}H NMR and Mass spectroscopy.[33,34]

IR spectra of compounds **5f** and **5g** reveals that, the (C=O) absorption bands were observed in the region 1654–1660 cm^{-1} and the (C=N) stretching was observed at 1595 cm^{-1} whereas in the IR spectra of compounds **6f** and **6g,** the (C=O) absorption bands were not observed in the region 1654–1660 cm^{-1} and the (C=N) stretching was found in the same region. These stretching vibration values confirm the formation of desired pyrazoline derivatives. In the ^{1}H NMR spectra of compounds **5f**, **5g** and **6f**, **6g**, the chiral CH proton appeared at δ 5.8–5.9 and 5.53–5.57, respectively as doublet of doublet, while the pro-chiral methylene protons appeared at δ 3.07–3.77 and δ 3.23–3.98 respectively as two distinct doublet of a doublet there by indicating the magnetic non-equivalency of the two protons. These newly synthesized compounds are also confirmed by mass spectral analysis.

All these newly synthesized pyrazoline derivatives were evaluated for their antiinflammatory activity[30] at 50 mg/kg p.o. against carrageenan induced paw edema method in wistar rats,[31] and compared with the standard drug Diclofenac sodium. The effects of synthesized compounds and standard drug on paw edema induced by carrageenan are shown in Table 1. The antiinflammatory result reveals that compounds **5g** and **6g** showed excellent activity whereas the compounds **5b**, **5c**, **5f**, **6b**, **6c** and **6f** showed significant activity after comparing with Diclofenac. The remaining pyrazoline derivatives showed weak antiinflammatory activity.

All these compounds were also evaluated for their analgesic activity at 25 mg/kg p.o. by radiant heat tail flick method in rats.[32] The results are summarized in Table 1 and are expressed as percentage analgesia. All compounds showed analgesic activity in the range of **35–110**% and were compared with the standard drug Aspirin. The analgesic result revealed that the compounds **5c**, **5d**, **5e**, **5f**, **6c**, **6d**, **6e**, and **6f** showed significant activity as compared with standard drug Aspirin, while as remaining compounds showed moderate analgesic activity after 1 h treatment.

The new series of fluoro substituted pyrazoline derivatives were synthesized using PEG-400 as an alternative reaction medium and identified as anti inflammatory and analgesic agents. The reaction was clean and the products were obtained in excellent yields without formation of any detectable side products. Among the 14 compounds screened, the four compounds **5c**, **5f**, **6c** and **6f** showed significant activities in both screens when compared to standard drugs Diclofenac and Aspirin. Hence, it can be concluded that, the tested pyrazolines derivatives can considered as potential anti-inflammatory and analgesic agents. Further studies in relation to cytotoxicity and ADME are warranted for the better understanding.

Acknowledgment

The author S.Y.J. is thankful to the University Grants Commission (WRO), Pune for the award Teacher Fellowship under XI plan.

References and notes

1. Kuznetsova, L.; Ungureanu, M. I.; Pepe, A. *J. Fluorine Chem.* **2004**, *125*, 415.
2. Haga, T.; Fujikawa, K.; Koyanag, T.; Nakajima, T.; Hayashi, K. *Heterocycles* **1984**, *22*, 117.
3. Patel, M. V.; Bell, R.; Majest, S.; Henry, R.; Kolasa, T. *J. Org. Chem.* **2004**, *69*, 7058.
4. Damlijanovic, I.; Vukicevic, M.; Radulovic, N.; Palic, R.; Ellmerer, E.; Ratkovic, Z.; Joksovic, M. D.; Vukicevic, R. D. *Bioorg. Med. Chem. Lett.* **2009**, *1093*, 19.
5. Sharma, P. K.; Kumar, S.; Kumar, P.; Kaushik, P.; Kaushik, D.; Dhingra, Y.; Aneja, K. R. *Eur. J. Med. Chem.* **2010**, *45*, 2650.
6. Sherif, A. F.; Rostom, M. A.; Shalaby, M. A.; El-Demellawy *Eur. J. Med. Chem.* **2003**, *38*, 959.
7. Mosafa, M. G.; Fatma, A. R.; Saleh, I. A.; Ahmed, M. A.; Sarah, A. A. *Eur. J. Med. Chem.* **2010**, *45*, 171.
8. Nikhila, D.; Amnekar, K. P.; Bhusari *Eur. J. Med. Chem.* **2010**, *45*, 149.
9. Ozdemir, Z.; Kandilici, H. B.; Gumusel, B.; Calis, U.; Bilgin, A. *Eur. J. Med. Chem.* **2007**, *42*, 373.
10. Shaharyar, M.; Siddique, A. A.; Ali, M. A.; Sriram, D.; Perumal, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3947.
11. Rathish, I. G.; Javed, K.; Ahmed, S.; Bano, S.; Alam, M. S.; Pillai, K. K.; Singh, S.; Bagchi, V. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 255.
12. Dawane, B. S.; Konda, S. G.; Mandwad, G. G.; Shaikh, B. M. *Eur. J. Med. Chem.* **2010**, *45*, 387.
13. Gulhan, T. H.; Pierre, C.; Fatma, S. K.; E. Kevser, E. *Eur. J. Med. Chem.* **2000**, *35*, 635.
14. Fioravanti, R.; Bolasco, A.; Manna, F.; Rossi, F.; Orallo, F.; Ortuso, F.; Alcaro, S.; Cirilli, R. *Eur. J. Med. Chem.* **2010**, *45*, 6135.
15. Joshi, R. S.; Mandhane, P. G.; Diwakar, S. D.; Dabhade, S. K.; Gill, C. H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3721.
16. (a) Amir, M.; Kumar, H.; Khan, S. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 918; (b) Desai, N. C.; Joshi, V. V.; Rajpara, K. M.; Vaghani, H. V.; Satodiya, H. M. *J. Fluorine Chem.* **2012**, *142*, 67.
17. Manfredini, S.; Bazzanini, R.; Baraldi, P. G.; Guarneri, M.; Simoni, D.; Marongiu, M. E.; Pani, A.; Colla, P. L.; Tramontano, E. *J. Med. Chem.* **1992**, *35*, 917.
18. Noell, C. W.; Cheng, C. C. *J. Med. Chem.* **1971**, *14*, 1245.
19. Abdel-Aziz, M.; Abuo-Rahma, G. A.; Hassan, A. A. *Eur. J. Med. Chem.* **2009**, *44*, 3480.
20. Bonesi, M.; Loizzo, M. R.; Statti, G. A.; Michel, S.; Tillequin, F.; Menichini, F. *Bioorg. Med. Chem. Lett.* **1990**, *2010*, 20.
21. Coutinho, E. C.; Khunt, R. C.; Khedkar, V. M.; Chawda, R. S.; Chauhan, N. A.; Parikh, A. R. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 666.
22. Shelke, S.; Mhaske, G.; Gadakh, S.; Gill, C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7200.
23. Suryakiran, N.; Ramesh, D.; Vemkateswarulu, Y. *Green Chem. Lett.* **2007**, *1*, 73.
24. Kamal, A.; Reddy, D. R.; Rajender, S. *Tetrahedron Lett.* **2005**, *46*, 7951.
25. Das, B.; Krishnaiah, M.; Balsubramanyam, P. *Tetrahedron Lett.* **2008**, *49*, 2225.
26. Olga, Biondi; Salvatore, Motta; Pasquale, Mosesso *Mutagenesis* **2002**, *17*, 261.
27. Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. *Green Chem.* **2005**, *7*, 64.
28. (a) Li, J. H.; Liu, W. J.; Xie, Y. X. *J. Org. Chem.* **2005**, *70*, 5409; (b) Jain, S. L.; Singhal, S.; Sain, B. *Green Chem.* **2007**, *9*, 740; (c) Han, W.; Liu, C.; Jin, Z.-L. *Org. Lett.* **2007**, *9*, 4005.
29. Kira, M. A.; Abdel-Raeman, M. O.; Gadall, K. Z. *Tetrahedron Lett.* **1969**, *2*, 109.
30. *Pharmacology*: *Wistar rat* of either sex weighing 150–220 g were obtained from Animal house, Luqman College of Pharmacy, Gulberga, Karnataka, India. All the animals were housed under standard ambient conditions of temperature (25 ± 2 °C) and relative humidity of 50 ± 5%. A 12/12 h light/dark cycle was maintained. All the animals were allowed to have free access to water and standard palletized laboratory animal diet 24 h before pharmacological studies. All experiments were carried out using six animals per group. The experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of Luqman College of Pharmacy, Gulberga, constituted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA/346), Government of India.
31. Muniappan, M.; Sundararaj, T. *J. Ethnopharmacol.* **2003**, *88*, 161.
32. Meena Kumari, K.; Amberkar, M. V.; Shanbhag, T.; Bairy, K. L.; Shenoy, S. *Indian J. Physiol. Pharmacol.* **2011**, *55*, 13.
33. *Synthesis of pyrazoline derivatives (**5a–g**)*: A mixture of pyrazole chalcones **4a–g** (1.0 mM) were placed in a 100 mL round bottom flask with 10 mL of PEG-400. To this solution hydrazine hydrate (99%) (2.0 mM) and 1 mL glacial acetic acid were added drop wise and heated at 70–75 °C for about 4–5 h. Reaction progress was monitored by TLC. After completion of the reaction, reaction mixture was cooled, poured into crushed ice, precipitate formed was filtered off and recrystallized from ethanol, affording compounds **5a–g**. Compound **5a**: yield: 80%; mp: 232–233 °C; IR (KBr) cm^{-1}: 3059, 1656, 1600, 1505, 1414, 1229; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, *N*-acetyl), 3.06 (dd, 1H, pyrazoline H), 3.57–3.69 (dd, 1H, pyrazoline H), 5.81–5.86 (dd, 1H, pyrazoline H), 7.07–7.76 (m, 13H, ArH), 7.78 (s, 1H, pyrazole-H). Compound **5b**: yield: 84%; mp: 228–230 °C; IR (KBr) cm^{-1}: 3059, 1656, 1600, 1505, 1414, 1229; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46 (s, 3H, *N*-acetyl), 3.05–3.10 (dd, 1H, pyrazoline H), 3.61–3.65 (dd, 1H, pyrazoline H), 5.85–5.88 (dd, 1H, pyrazoline H), 7.10–7.73 (m, 13H, ArH), 7.80 (s, 1H, pyrazole-H); MS: *m*/*z* = 459 (M+1). Compound **5c**: yield: 78%; mp: 213–214 °C; IR (KBr) cm^{-1}: 3062, 1657, 1599, 1505, 1415, 1229; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, *N*-acetyl), 3.01–3.08 (dd, 1H, pyrazoline H), 3.61–3.65 (dd, 1H, pyrazoline H), 5.82–5.87(dd, 1H, pyrazoline H), 7.07–7.68 (m, 13H, ArH), 7.78 (s, 1H, pyrazole-H); MS: *m*/*z* = 505 (M+2). Compound **5d**: yield: 85%; mp: 198 °C; IR (KBr) cm^{-1}: 3192, 2915, 2839, 1648,1595,1501, 1407, 1222; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, $-CH_3$) 2.44 (s, 3H, *N*-acetyl), 3.02–3.09 (dd, 1H, pyrazoline H), 3.54–3.64 (dd, 1H, pyrazoline H), 5.87–5.92 (dd, 1H, pyrazoline H), 7.04–7.69 (m, 13H, ArH), 7.76 (s, 1H, H-5 of pyrazole); MS: *m*/*z* = 439 (M+1). Compound **5e**: yield: 83%; mp: 162–164 °C; IR (KBr) cm^{-1}: 2995, 2892,1660, 1601, 1507,1359, 1239, 1154, 1052; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46 (s, 3H, *N*-acetyl), 3.83 (s, 3H, $-OCH_3$), 3.06–3.1(dd, 1H, pyrazoline H), 3.58–3.63 (dd, 1H, pyrazoline H), 5.87–5.91 (dd, 1H, pyrazoline H), 6.95–7.71 (m, 13H, ArH), 7.79 (s, 1H, pyrazole-H); MS: *m*/*z* = 455 (M+1). Compound **5f**: yield: 74%; mp: 247–248 °C; IR (KBr) cm^{-1}: 2995, 2892, 1660, 1595, 1507, 1359, 1239, 1154, 1052; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, *N*-acetyl), 3.07–3.14 (dd, 1H, pyrazoline H), 3.68–3.77 (dd, 1H, pyrazoline H), 5.83–5.88 (dd, 1H, pyrazoline H), 7.07–8.60 (m, 13H, ArH), 7.79 (s, 1H, pyrazole-H). Compound **5g**: yield: 85%; mp:174–175 °C; IR (KBr) cm^{-1}: 3010, 1654, 1595, 1503, 1240; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H,

N-acetyl), 3.03–3.10 (dd, 1H, pyrazoline H), 3.56–3.66 (dd, 1H, pyrazoline H), 5.87–5.92 (dd, 1H, pyrazoline H), 7.05–7.76 (m, 14H, ArH), 7.78 (s, 1H, pyrazole-H); MS: m/z = 425 (M+1).

34. *Synthesis of pyrazoline derivatives (**6a–g**)*: A mixture of pyrazole chalcones **4a–g** (1.0 mM) were placed in a 100 mL round bottom flask with 10 mL of PEG-400. To this solution phenyl hydrazine (1.0 mM) and 40% NaOH (2 mL) were added drop wise and heated at 70–75 °C for about 4–5 h depending upon the substituent's present in the compound. Reaction progress was monitored by TLC. After completion of the reaction, reaction mixture was cooled, poured into crushed ice, precipitate formed was filtered off and recrystallized from ethanol, affording compounds **6a–g**. Compound **6a**: yield: 82%; mp: 170–172 °C; IR (KBr) cm^{-1}: 3057, 1595, 1495, 1455, 1380, 1322, 1220; ^1H NMR (500 MHz, $CDCl_3$): δ 3.19–3.24 (dd, 1H, $-CH_2-$ pyrazoline H); 3.82–3.90 (dd, 1H, $-CH_2-$ pyrazoline H); 5.49–5.52 (dd, 1H, –CH– pyrazoline H); 6.84–7.79 (m ,18H, Ar-H); 7.90 (s, 1H, pyrazole-H). Compound **6b**: yield: 80%; mp: 156–157 °C; IR (KBr) cm^{-1}: 3055, 1596, 1497, 1384, 1323, 1221; ^1H NMR (500 MHz, $CDCl_3$): δ 3.19–3.24 (dd, 1H, $-CH_2-$ pyrazoline H); 3.82–3.85 (dd, 1H, $-CH_2-$ pyrazoline H); 5.49–5.52 (dd, 1H, –CH– pyrazoline H); 6.83–7.78 (m, 18H, Ar-H); 7.80 (s, 1H, pyrazole-H); MS: m/z = 493 (M+1). Compound **6c**: yield: 79%; mp: 138–140 °C; IR (KBr) cm^{-1}: 3049, 1594, 1493, 1385, 1325, 1218; ^1H NMR (500 MHz, $CDCl_3$): δ 3.19–3.23 (dd, 1H, $-CH_2-$ pyrazoline H); 3.82–3.87 (dd, 1H, $-CH_2-$ pyrazoline H); 5.49–5.52 (dd, 1H, –CH– pyrazoline H); 6.83–7.73 (m, 18H, Ar-H); 7.82 (s, 1H, pyrazole-H). Compound **6d**: yield: 86%; mp: 185–186 °C; IR (KBr) cm^{-1}: 3019, 2924, 1595, 1496, 1383, 1321, 1216; ^1H NMR (500 MHz, $CDCl_3$): δ 2.46 (s, 3H, Methyl H); 3.21-3.26 (dd, 1H, $-CH_2-$ pyrazoline H); 3.82–3.88 (dd, 1H, $-CH_2-$ pyrazoline H); 5.52–5.55 (dd, 1H, –CH– pyrazoline H); 6.82–7.74 (m, 18H, Ar-H); 7.78 (s, 1H, pyrazole-H); MS: m/z = 473 (M+1). Compound **6e**: yield: 88%; mp: 168 °C; IR (KBr) cm^{-1}: 3025, 2994, 1598, 1498, 1453, 1388, 1292; ^1H NMR (500 MHz, $CDCl_3$): δ 3.91 (s, 3H, Methoxy H); 3.21–3.26 (dd, 1H, $-CH_2-$ pyrazoline H); 3.81–3.87 (dd, 1H, $-CH_2-$ pyrazoline H); 5.50–5.53 (dd, 1H, –CH– pyrazoline H); 6.82–7.76 (m, 18H, Ar-H); 7.78 (s, 1H, pyrazole-H); MS: m/z = 489 (M+1). Compound **6f**: yield: 78%; mp: 242–244 °C; IR (KBr) cm^{-1}: 3058, 1595, 1528, 1497, 1344, 1220; ^1H NMR (500 MHz, $CDCl_3$): δ 3.24–3.29 (dd, 1H, $-CH_2-$ pyrazoline H); 3.92–3.98 (dd, 1H, $-CH_2-$ pyrazoline H); 5.54–5.57 (dd, 1H, –CH– pyrazoline H); 6.83–8.69 (m, 18H, Ar-H); 7.87 (s, 1H, pyrazole-H). Compound **6g**: yield: 86%; mp: 150–152 °C; IR (KBr) cm^{-1}: 3059, 1594, 1495; 1374, 1217; ^1H NMR (500 MHz, $CDCl_3$): δ 3.23–3.27 (dd, 1H, $-CH_2-$ pyrazoline H); 3.83-3.89 (dd, 1H, $-CH_2-$ pyrazoline H); 5.53–5.57 (dd, 1H, –CH– pyrazoline H); 6.82–7.84 (m, 19H, Ar-H); 7.80 (s, 1H, pyrazole-H); MS: m/z = 459 (M+1).