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# Synthesis, Characterization and Biological Evaluation of Some Arylazopyrazoles

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1-[(N-Acetyl)2,5-dichloroanilinomalonyl]3,5-dimethyl-4-(unsubstituted/substituted phenylazo) pyrazoles have been synthesised in 31-65 % yield, by the reaction of 2,4-diketo-3- (unsubstituted/substituted phenylazo) pentane with ethyl-2-[(N-acetyl)2,5-dichloroanilido] acetohydrazide. Pyrazoles are brown and yellow colour solids, having high melting points. Identity of products has been established by elemental analysis and spectral data. Newly synthesized compounds [**5a-t**] have been tested for their antibacterial activity against gram positive bacteria *S. albus*, *S. aureus* and gram negative bacteria *E. coli* and *Pseudomonas piosineus*. The compound **5a, 5c, 5d, 5e, 5g** and **5h** show significant activity and compound **5b, 5f, 5i, 5j, 5k, 5n** and **5p** have shown moderate activity. The same compounds were tested for their antifungal activity against *Candida albicans*, *Aspergillus niger* and *Alternaria alternata* at 30 mg/mL concentration using sabouraud dextrose agar media. Compounds **5a, 5c, 5d** and **5g** were found to be moderately active against *Candida albicans* and *Aspergillus niger*. All the other compounds did not show significant activity against the fungi at this concentration.

**Key Words: Arylazopyrazoles, Synthesis, Characterization and Biological activities.**

## INTRODUCTION

Pyrazoles and their derivatives are important on account of use in therapy in different diseases[1-8] antibacterial[9-13], fungicidal[14-20], antidiuretic[21,22], anticancer[23-28] and anti HIV[16,29-31] antitumour[32], antianalgesic-inflamatory[12,33-36], anticonvulsant[37] properties of pyrazoles have been reported in the literature. Synthesis and interesting aspect of biological activity of arylazopyrazoles have been reported[38,39]. In view of potential biological activities of pyrazoles and arylazopyrazoles we report here the synthesis of some 1-[(N-acetyl) 2,5-dichloro anilinomalonyl]3,5-dimethyl-4-(unsubstituted/substituted phenylazo) pyrazoles. The present communication deals with the reaction of acetyl acetone with diazotised aromatic primary amine in presence of sodium acetate which furnished 2,4-diketo-3-(unsubstituted/substituted phenylazo) pentanes (**I**) which on treatment with ethyl-2-[(N-acetyl)2,5-dichloroanilido]

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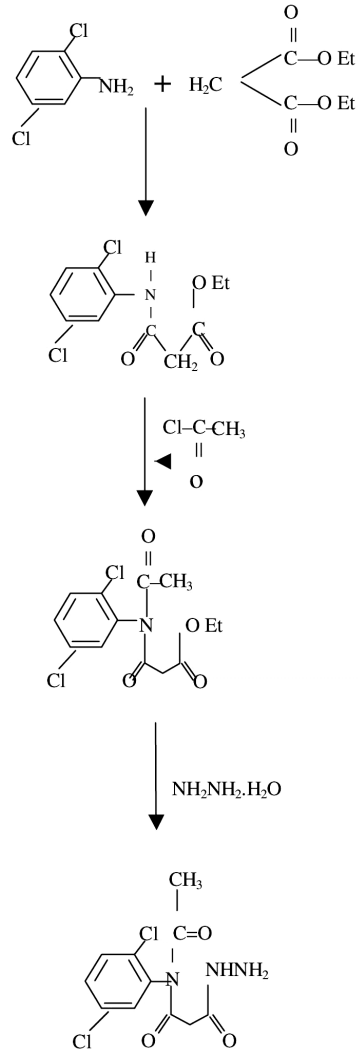
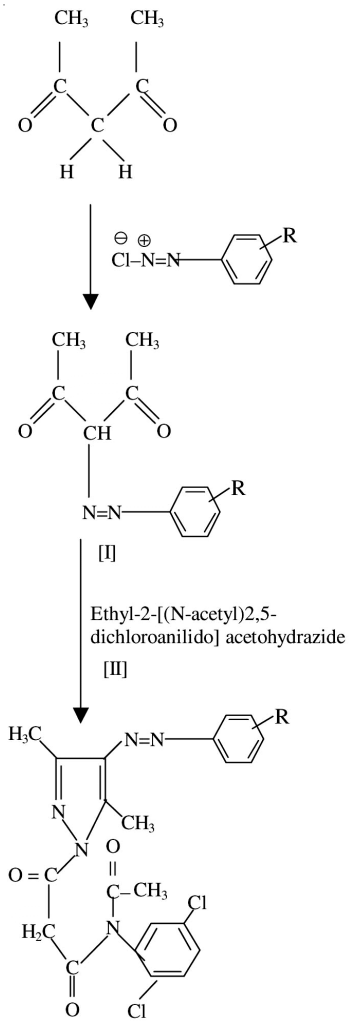
acetohydrazide (**II**) in acetic acid medium resulted in the formation of 1-[(N-acetyl) 2,5-dichloro anilinomalonyl]3,5-dimethyl-4-(unsubstituted/substituted phenylazo) pyrazoles (**5a-t**) in varying yield 31-65 % (Table-1). Antibacterial and antifungal activities of new arylazopyrazoles were investigated.




**Schemne-I**




**Scheme-II**

## EXPERIMENTAL

All the chemicals were used for synthesis are of analytical reagent grade. Melting points are taken in open capillaries and are uncorrected. Purity of the compounds was checked by TLC. All the compounds gave satisfactory elemental analysis. IR

Spectra were recorded on a Perkin-Elmer spectrum RX1 FT IR spectrophotometer using KBr pallatisation technique and NMR spectra were recorded on Bruker DRX-300 NMR spectrophotometer. The NMR peaks were recorded on δ scale (ppm) against TMS. The solvent employed was DMSO (3.33-3.35 δ). The elemental analysis of all the compounds done on Elementar vario EL III Carlo Erba 1108. 2,4-Diketo-3-(unsubstituted/substituted phenylazo) pentane were synthesized by reported method[40]. Ethyl-2-[(N-acetyl)2,5-dichloroanilido]acetohydrazide was prepared by the procedure given by Rathore and Ittyerah[41].

TABLE-1

| CS. No. | R | Colour | m.p. (ºC) | Yield (%) | m.f. |
|---|---|---|---|---|---|
| **5a** | H | Yellow | 271 | 65 | $C_{27}H_{21}N_5O_3Cl_2$ |
| **5b** | $CH_3$ (*o*) | Light Yellow | 263 | 60 | $C_{28}H_{23}N_5O_3Cl_2$ |
| **5c** | $CH_3$ (*m*) | Yellow | 244 | 53 | $C_{28}H_{23}N_5O_3Cl_2$ |
| **5d** | $CH_3$ (*p*) | Light Yellow | 239 | 51 | $C_{28}H_{23}N_5O_3Cl_2$ |
| **5e** | Cl (*o*) | Yellow | 273 | 54 | $C_{27}H_{20}N_5O_3Cl_3$ |
| **5f.** | Cl (*m*) | Yellow | 256 | 49 | $C_{27}H_{20}N_5O_3Cl_3$ |
| **5g** | Cl (*p*) | Light Yellow | 272 | 52 | $C_{27}H_{20}N_5O_3Cl_3$ |
| **5h** | $OCH_3$ (*o*) | Light Yellow | 266 | 55 | $C_{28}H_{23}N_5O_4Cl_2$ |
| **5i** | $OCH_3$ (*m*) | Yellow | 259 | 40 | $C_{28}H_{23}N_5O_4Cl_2$ |
| **5j** | $OCH_3$ (*p*) | Light Yellow | 273 | 46 | $C_{28}H_{23}N_5O_4Cl_2$ |
| **5k** | F (*p*) | Yellow | 249 | 32 | $C_{27}H_{20}N_5O_3Cl_2$ |
| **5l** | Br (*o*) | Dark brown | 259 | 61 | $C_{27}H_{20}N_5O_3BrCl_2$ |
| **5m** | $OC_2H_5$ (*o*) | Brown | 265 | 44 | $C_{29}H_{25}N_5O_4Cl_2$ |
| **5n** | $OC_2H_5$ (*m*) | Brown | 252 | 46 | $C_{29}H_{25}N_5O_4Cl_2$ |
| **5o** | $OC_2H_5$ (*p*) | Brown | 244 | 43 | $C_{29}H_{25}N_5O_4Cl_2$ |
| **5p** | $CO_2H$ (*o*) | Brown | 258 | 36 | $C_{28}H_{22}N_5O_5Cl_2$ |
| **5q** | $CO_2H$ (*m*) | Brown | 243 | 39 | $C_{28}H_{22}N_5O_5Cl_2$ |
| **5r** | $CO_2H$ (*p*) | Light brown | 265 | 41 | $C_{28}H_{22}N_5O_5Cl_2$ |
| **5s** | Br (*m*) | Brown | 238 | 36 | $C_{27}H_{20}N_5O_3BrCl_2$ |
| **5t** | Br (*p*) | Brown | 247 | 31 | $C_{27}H_{20}N_5O_3BrCl_2$ |

All compounds gave satisfactory elemental analysis.

**Synthesis of ethyl-2-[2,5-dichloroanilido] ethanoate (1):** A mixture of 2,5-dichloro aniline (10 mL) and diethyl malonate (20 mL) was refluxed for 45 min in a round bottomed flask fitted with an air condenser of such a length (14") that ethanol formed escaped and diethyl malonate flowed back into the flask. Contents were cooled, ethanol (30 mL) was added, when malon-2,5-dichlorodianilide separated out. It was filtered under suction. The filtrate was poured on to crushed ice (*ca.* 160 g) and stirred when ethyl-2-(2,5-dichloroanilido) ethanoate precipitated as green mass. On recrystallization from aqueous ethanol (50 %), ester was obtained as white crystals. Yield; 78 %, m.p. 83 ºC, m.w. 276. Anal. calculation for $C_{11}H_{11}NO_3Cl_2$: Found. (%) C 39.20, H 03.24, N 4.14, Cl 21.09, calcd. (%): C 39.21, H 3.26, N 4.15, Cl 21.04. IR [KBr, $\nu_{max}$, $cm^{-1}$]: 1665-1660 [C=O diketone], 1290 [-C-O- ester],

760-755 [2,5-di substituted benzene], 1250 [C-Cl Stretching], 1590, 1520, 1440 [C=C ring stretching], 3150 [N-H stretching], 3040 [C-H aromatic], 1330-1322 [C-H stretching]. PMR (DMSO): δ 4.42 (2H, s, CO-$CH_2$-CO), 4.0 (2H, s, $NH_2$), 7.4-8.6 (3H, m, Ar-H), 9.2 (1H, s, CO-NH $D_2O$ exchangeable), 10.6 [1H, s, Ar-NH, $D_2O$ exchangeable].

**Synthesis of ethyl-2-[(N-acetyl) 2,5-dichloroanilido] ethanoate (2):** Acetyl chloride (4.74 g; 0.06 mol), dioxane (6 mL), ethyl-2-(2,5-dichloroanilido) ethanoate (16.56 g; 0.06 mol) and triethyl amine (5.7 g; 0.06 mol) were placed in a round bottomed flask carrying reflux condensor having calcium chloride guard tube. The contents were heated on a boiling water bath for 2 h and kept over night when triethyl amine hydrochloride separated. It was filtered under suction and the filtrate was poured on to crushed ice (*ca.* 180 g) and stirred when ethyl-2-[(N-acetyl) 2,5-dichloroanilido]ethanoate separated and solidified. It was filtered under suction, dried and purified by recrystallization from aqueous methanol (1:1) in white crystals. Yield = 75.4 %, m.p. 90 °C. Anal. calculation for $C_{13}H_{13}NO_4Cl_2$: [m.w. 318], calcd. (%): N 2.95, C 45.64, H 3.38, Cl 15.00, found. (%): N 2.94, C 45.62, H 3.37, Cl 15.02. IR [KBr, $\nu_{max}$, $cm^{-1}$]: 1720 [C=O diketone], 1300 [-C-O- ester], 762 [2,5-disubstituted benzene], 1090 [C-Cl stretching], 1590, 1520, 1440 [C=C ring stretching], 3160 [N-H stretching], 3040 [C-H aromatic], 1330-1322 [C-H stretching]. PMR (DMSO): δ 4.44 [2H, s, CO-$CH_2$-CO], 4.1 [2H, s, $NH_2$], 7.2-8.5 [3H, m, Ar-H], 9.4 [1H, s, CO-NH $D_2O$ exchangeable], 10.8 [1H, s, Ar-NH $D_2O$ exchangeable].

**Synthesis of ethyl-2-[(N-acetyl)2,5-dichloroanilido]acetohydrazide (3):** Ethyl-2-[(N-acetyl)2,5-dichloroanilido]ethanoate (9.54 g; 0.03 mol), ethanol (10 mL) and hydrazine hydrate (15 mL; 80 %) were mixed together and stirred for 35 min. Ethyl-2-[(N-acetyl)2,5-dichloroanilido]acetohydrazide was filtered under suction and recrystallized from ethanol in white crystals. Yield 79 %, m.p. 177 °C, m.w. 304: anal. calculation for $C_{11}H_{11}N_3O_3Cl_2$: calcd.: N 9.04, C 41.32, H 3.01, Cl 15.28, found. (%): N 9.01, C 41.30, H 3.00, Cl 15.27. IR [KBr, $\nu_{max}$, $cm^{-1}$]: 3160 [N-H stretching], 3048 [C-H aromatic], 1660 [C=O diketone], 1432 [C-Cl aromatic], 1595, 1520, 1445 [C=C ring stretching]. PMR (DMSO): δ 4.44 (2H, s, CO-$CH_2$-CO), 4.1 (2H, s, $NH_2$), 7.2-8.5 (3H, m, Ar-H), 9.4 (1H, s, CO-NH $D_2O$ exchangeable), 10.7 (1H, s, Ar-NH $D_2O$ exchangeable).

**Synthesis of 2,4-diketo-3-(phenylazo) pentane (R=H) (4):** Aniline (9.3 mL, 0.1 mol) was dissolved in aqueous hydrochloric acid (80 mL, 1:1). The contents were stirred, cooled (0-2 °C) and cold solution of sodium nitrite (12 g in 30 mL water) was slowly added maintaining the temperature between 0-2 °C. The cold diazotized solution was added dropwise with stirring to a well cooled mixture of acetylacetone (0.1 mol, 10 mL) and sodium acetate (12 g dissolved in 10 mL of 50 % aqueous ethanol). Stirring was further continued for 45 min, when yellow crystals separated. The product was filtered under suction, washed with water and recrystallized from aqueous ethanol. Analytical (%) for $C_{11}H_{12}N_2O_2$: found. (%): C 38.17, H 3.47, N 8.09, calcd. (%): C 38.16, H 3.46, N 8.00, yield; 62 %, m.p. 96 °C, [m.w.

204], other 2,4-diketo-3-(unsubstituted/substituted phenylazo) pentanes were prepared by above mentioned procedure.

**Synthesis of 1-[(N-acetyl)2,5-dichloroanilinomalonyl]3,5-dimethyl-4-phenylazo)pyrazoles (5):** 2,4-diketo-3-(phenylazo)pentane (0.204 g, 0.001 mol) and ethyl-2-[(N-acetyl)2,5-dichloroanilido] acetohydrazide (0.305 g, 0.001 mol) were dissolved in glacial acetic acid (10 mL) and the solution was refluxed for 14 h. The resulting solid was purified by repeated washing with acetic acid and recrystallized from acetic acid as yellow crystals. Yield 46 %, m.p. 263 °C analysis (%): found. (%): N 7.55, Cl 7.14 $C_{22}H_{19}N_5O_3Cl_2$ [m.w. 472], calcd. (%) N 7.56, Cl 7.16. IR (KBr, $\nu_{max}$, $cm^{-1}$): 3268-3062 (N-H sec. amide hydrogen bond), 2970 (C-H stretching aromatic), 1660 (C=N pyrazole), 1550 (C=C aromatic), 1056 (C-Cl aromatic). PMR (DMSO): δ 2.36 (2H, s, $CH_2$), 4.14 (1H, s, NH), 6.90-7.05 S(7H, s, Ar-H). Other 1-[(N-acetyl)2,5-dichloroanilinomalonyl]3,5-dimethyl-4-((unsubstituted/substituted phenylazo) pyrazoles were prepared by above mentioned procedure.

**Biological activities**

**Antibacterial activity:** Newly synthesized compounds (**5a-t**) have been tested for their antibacterial activity against gram positive bacteria *S. albus*, *S. aureus* and gram negative bacteria *E. coli* and *Pseudomonas piosineus* by agar plate disc diffusion method at 30 μg/mL concentration. Ampicillin and tetracycline were used as a reference compounds. The compound **5a, 5c, 5d, 5e, 5g** and **5h** shown significant activity and compound **5b, 5f, 5i, 5j, 5k, 5n** and **5p** have shown moderate activity.

**Antifungal activity:** The same compounds were tested for their antifungal activity against *Candida albicans*, *Aspergillus niger* and *Alternaria alternata* at concentration of 30 mg/mL using sabouraud dextrose agar media. Compounds **5a, 5c, 5d** and **5g** were found to be moderately active against *Candida albicans* and *Aspergillus niger*. All the other compounds did not show significant activity against the fungi at this concentration.

## RESULTS AND DISCUSSION

1-[(N-Acetyl)2,5-dichloroanilinomalonyl]3,5-dimethyl-4-(unsubstituted/substitutedphenylazo) pyrazoles have been synthesised by the reaction of 2,4-diketo-3-(unsubstituted/substituted phenylazo) pentane with ethyl-2-[(N-acetyl)2,5-dichloroanilido] acetohydrazide in 31-65 % yield. Pyrazoles are brown and yellow colour solids, having high melting points. The structure of all the compounds are confirmed by IR, PMR and mass spectral data and are further supported by correct elemental analysis (experimental part). All the newly synthesized compounds (**5a-t**) have been screened for their antibacterial activity against gram positive bacteria *S. albus*, *S. aureus* and gram negative bacteria *E. coli* and *Pseudomonas piosineus*. The compound **5a, 5c, 5d, 5e, 5g** and **5h** shown significant activity and compound **5b, 5f, 5i, 5j, 5k, 5n** and **5p** have shown moderate activity. The same compounds were screened for their antifungal activity against *Candida albicans*, *Aspergillus*

*niger* and *Alternaria alternata* at concentration of 30 mg/mL using sabouraud dextrose agar media. Compounds **5a, 5c, 5d** and **5g** were found to be moderately active against *Candida albicans* and *Aspergillus niger*. All the other compounds did not show significant activity against the fungi at this concentration.

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## REFERENCES

1. H.M. El. Shaaer, *Mansoura Sci. Bull. A Chem*., **S24**, 171 (1997).
2. S. Francesco and B. Alessandro, *Farmaco*, **51**, 141 (1996).
3. P. Chandra, G.S. Saharia and H.R. Sharma, *J. Indian Chem. Soc.*, **54**, 381 (1977).
4. S.A. El-Hawash, N.S. Habib and M. Kassem, *Arch. Pharm. Chem. Life Sci.*, **339**, 564 (2006).
5. U. Salgin-Goksen, N. Gokhan-Kelekci, O. Goktas, Y. Koysal, E. Kihc, S. Isik, G. Aktay and M. Ozalp, *Bioorg. Med. Chem*., **15**, 5738 (2007).
6. A. Kumar, D. Bansal, K. Bajaj, S. Sharma and V.K.A. Shrivastava, *Bioorg. Med. Chem.*, **11**, 5281 (2003).
7. N. Gökhan-Kelekçi, S. Yabanoglu, E. Küpeli, U. Salgin, Ö. Özgen, G. Uçar, E. Yesilada, E. Kendi, A. Yesilada and A.A. Bilgin, *Bioorg. Med. Chem*., **15**, 5775 (2007).
8. G.S. Godaginamath, S.R. Pujar and R.R. Kavali, *Indian J. Chem*., **42B**, 2023 (2003).
9. G.S. Saharia and H.R. Sharma, *Indian J. Chem*., **14B**, 626 (1976).
10. G.S. Godaginamath, S.R. Pujar, M.G. Bhovi and C.M. Kamanavalli, *Indian J. Heterocycl. Chem*., **13**, 209 (2004).
11. M.A. Abdallah, S.M. Riyadh, I.M. Abbas and S.M.Gomha, *J. Chin. Chem. Soc.*, **52**, 987 (2005).
12. A.A. Bekhit and T. Abdel-Aziem, *Bioorg. Med. Chem*., **12**, 1935 (2004).
13. S.A. Rostom, *Bioorg. Med. Chem*., **19**, 6475 (2006).
14. M.H.E. Elgandi, M.R.H. Elamoghayer, E.A.A. Hafer and H.H. Alniwa, *J. Org. Chem*., **40**, 2604 (1975).
15. S. Rollas, N. Gulerman and H. Erdeniz, *Farmaco*, **57**, 171 (2002).
16. N.A. Salih, *Turk. J. Chem*., **32**, 229 (2008).
17. R.A. Devasia, T.F. Jones, J. Ward, L. Stafford, H. Hardin, C. Bopp, M. Beatty, E. Mintz and W. Schaffner, *Am. J. Med*., **119**, 168 (2006).
18. H.I. Shaheen, S.B. Khalil, M.R. Rao, R.A. Elyazeed, T.F. Wierzba, L.F. Peruski, S. Putnam, A. Navarro, B.Z. Morsy, A. Cravioto, J.D. Clemens, A.M. Svennerholm and S.J. Savarino, *Egypt. J. Clin. Microbiol*., **42**, 5588 (2004).
19. K.A. Metwally, L.M. Abdel-Aziz, S.M. Lashine El., M.I. Husseiny and R.H. Badawy, *Bioorg. Med. Chem*., **14**, 8675 (2006).
20. P. Vicini, F. Zani, P. Cozzini and I. Doytchinova, *Eur. J. Chem*., **37**, 553 (2002).
21. A.A. Farghaly, A.A. Bekhit and J.Y. Park, *Arch. Pharm*., **333**, 53 (2000).
22. R. Wang, X. Lu, X. Yu, L. Shi and Y. Sun, *J. Mol. Catal. A: Chem*., **266**, 198 (2007).
23. S.A. Rostom, *Bioorg. Med. Chem*., **14**, 6475 (2006).
24. B.S. Holla, B.S. Rao, B.K. Sarojini, P.M. Akberali and N.S. Kumari, *Eur. J. Med. Chem*., **41**, 657 (2006).

25. T.S. Jeong, K.S. Kim, J.R. Kim, K.H. Cho, S. Lee and W.S. Lee, *Bioorg. Med. Chem. Lett*., **14**, 2719 (2004).
26. R. Lin, G. Chiu, Y. Yu, P.J. Connolly, S. Li, Y. Lu, M. Adams, A.R. Fuentes-Pesquera, S.L. Emanuel and L.M. Greenberger, *Bioorg. Med. Chem. Lett.*, **17**, 4557 (2007); DOI: 10.1016/ j.bmcl.(2007).05.092.
27. B.S. Holla, B.K. Sarojini, B.S. Rao, P.M. Akberali, N.S. Kumari and V. Shetty, *Farmaco*, **56**, 565 (2001).
28. I. Chaaban, El-Sayeda EL-Khawass, M. Mohran, O. EL-Sayed, H. EL-Saidi and H. Aboul-Enen, *Med. Chem. Res*., **15** (2007).
29. V.S. Jolly, M. Pathak and R. Jain, *Indian J. Chem.*, **32B**, 505 (1993).
30. V. Dhingra, R. Bhatnadekar and S. Perdse, *Indian J. Chem.*, **5**, 515 (1993).
31. S.M. Rida, F.A. Ashour, S.A. El-Hawash, M.M. Elsemary, M.H. Badr and M.A. Shalaby, *Eur. J. Med. Chem*., **40**, 949 (2005).
32. U. Salgin-Goksen, N. Gokhan-Kelekci, O. Goktas, Y. Koysal, E. Kihc, S. Isik, G. Aktay and M. Ozalp, *Bioorg. Med. Chem*., **15**, 5738 (2007).
33. H.O. Gulcan, E. Kupeli, S. Unlu, E. Yesilada and M.F. Sahin, *Arch. Pharm*., **336**, 477 (2003).
34. G.S. Godaginamath and D.S. Donawade, *Indian J. Chem*., **42B**, 3108 (2003).
35. A. Kumar, D. Bansal, K. Bajaj, S. Sharma and V.K. Archana Shrivastava, *Bioorg. Med. Chem*., **11**, 5281 (2003).
36. A.U. Tosun, A.E. Geciken, M. Goke, E. Yildirim and M.F. Sahin, *Turk. J. Pharm. Sci.*, **5**, 155 (2008).
37. T. Onkol, M.F. Sahin, E. Yildirim, K. Erol and S. Ito, *Arch. Pharm Res*., **27**, 1068 (2004).
38. V.K. Ahluwalia, U. Dutta and H.R. Sharma, *J. Indian Chem. Soc*., **64**, 221 (1987).
39. K.P. Sharma and H.K. Sharma, *Asian J. Chem*., **19**, 4129 (2007).
40. P. Phatak, Ph.D. Thesis, Jiwaji University, Gwalior, India (1996).
41. B.S. Rathore and P.I. Ittyerah, *J. Indian Chem. Soc*., **37**, 591 (1960).

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