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Synthesis and biological activity of some novel β-diketones containing pyrazole moiety†

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Abstract : Reaction of substituted pyrazole-1-acetyl chloride (3) with acetophenone derivative (4) in presence of sodium methoxide in dry toluene led to the synthesis of substituted β-diketones containing pyrazole moiety (5a-l). All the newly synthesized compounds were confirmed by elemental analysis and IR, ^{1}H, ^{13}C NMR and mass spectral studies. The compounds (5a-l) were evaluated for their antibacterial and antifungal activities.

Keywords : Acetophenone derivative, pyrazole-1-acetyl chloride, 1,3-diketones, sodium methoxide, antibacterial, antifungal activity.

Introduction

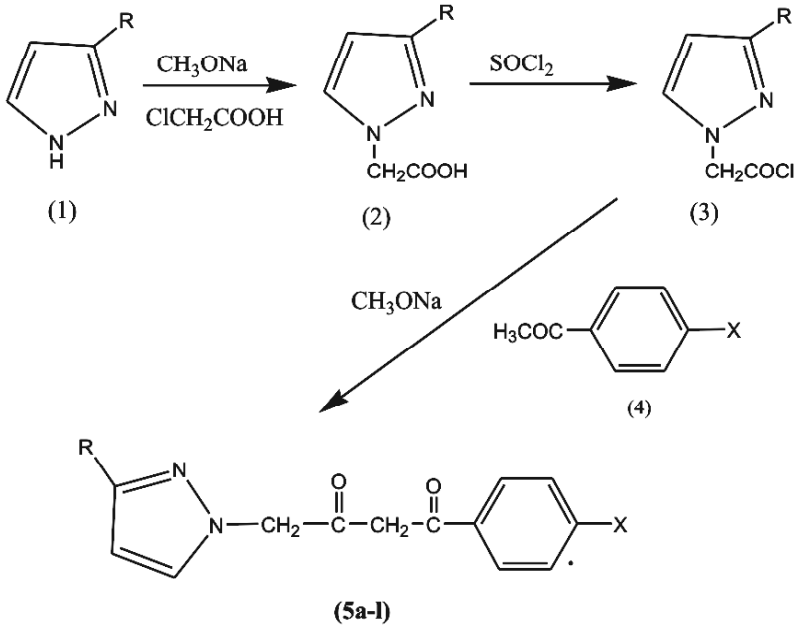
Pyrazoles are five member ring heterocyclic compounds, having two nitrogen atoms in adjacent position and are also called as azoles[1]. Pyrazole derivatives are known to exhibit a wide range of biological properties, such as anti-inflammatory[2–6], antioxidant[7], antimicrobial[8], anticancer,[9] fungicidal[10] and antiviral activities[11]. Some pyrazole derivatives were reported to possess high affinity and selectivity towards A 2b adenosine receptor antagonists[12]. Recently pyrazole derivatives have been found in nature[1] namely β-[1-pyrazolyl]alanine was isolated from the seeds of water melons (*Citrullus lanatus*). Particularly, aryl pyrazoles are important in medicinal and pesticidal chemistry[13]. Some aryl pyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity[14]. Also, it was reported that pyrazole-4-carboxylic acid hydrazides and corresponding hydrazones possess antimicrobial activity[15]. Several pyrazole derivatives are also effective against the metabolism sehistosomiasis in snozils[16,17]. Their derivatives have got significant biological properties as antithrombotic medicament (treatment of angina, pulmonary, hypertension, congestive heartfailure, arteriosclerosis, peripheral vascular disease, stroke bronchitis, alvegia)[18], antiproliferative agents[19], antidiabetes and also useful in Alzheimers disease[20]. They are useful intermediates for many industrial products[21,22].

β-Diketones serve as precursors for the synthesis of large number of pharmacologically active heterocyclic compounds such as diazepines[23], benzodiazepines[24], benzothiazepines[25], benzothiazines[26], pyrazoles[27], imidazoles and benzimidazole[28]. β-Diketones are powerful nature antioxidant[29], anticoagulant[30] and possess prominant anticancer properties with minimal toxicity[31,32]. In this report some new 1,3-diketone compounds containing pyrazole moiety were prepared with this hope that they may be have some potential antibacterial and antifungal properties.

Results and discussion

1,3-Diketone compounds containing pyrazole moiety (**5a-l**) were prepared by the reaction of pyrazole-1-acetyl chloride (**3**) with substituted acetophenones (**4**) in presence of sodium methoxide in dry toluene (Scheme 1). The structures of these compounds (**5a-l**) were determined by elemental analysis and IR, ^{1}H NMR, ^{13}C NMR and

†**In honour of Professor K. C. Joshi on the occasion of his 88th birthday.**



Scheme 1. Synthesis of substituted 1-phenyl-4-(pyrazol-l-yl)-butane-1,3-diones.

mass spectral studies. The physical data of these compounds **(5a-l)** are shown in Table 1.

The IR spectrum of compound (**5a**) showed characteristic absorption at 1740 cm^{-1} due to one carbonyl group and 1690 cm^{-1} due to another carbonyl group, which is downfield compared to normal >C=O stretching band. This downfield shift is due to extended conjugation of the carbonyl group with the aryl group. Other characteristic absorption peaks are observed at 3050 cm^{-1} (Ar-H stretch), 2890 cm^{-1} (C-H stretch of CH_2 group) and 1585 cm^{-1} due to C=N stretch. The ^1H NMR spectrum of **5a** showed multiplets between δ 8.16–6.50 due to eight aromatic protons, a singlet at δ 6.47 for two protons of methylene group which is attached to carbonyl groups and another singlet at δ 4.80 accounted for another methylene protons. The ^{13}C NMR spectrum of **5a** showed two peaks at δ 196.9 and 192.0 due to carbonyl carbons. Other peaks between δ 105–141 were observed due to aromatic carbons and peaks at δ 47.2, δ 65.7 were due to methylene carbons. The mass spectrum of compound **5a** showed a molecular ion peak at *m/z* 228 which is in conformity with the molecular formula $C_{13}H_{12}N_2O_2$.

Table 1. Physical and analytical data of compounds (**5a-l**)

Compd.	R	X	M.p. (°C)	Yield (%)
5a	H	H	168	56
5b	H	CH_3	175	51
5c	H	OCH_3	181	58
5d	H	Cl	183	49
5e	H	Br	180	54
5f	H	NO_2	165	50
5g	CH_3	H	170	54
5h	CH_3	CH_3	165	50
5i	CH_3	OCH_3	175	55
5j	CH_3	Cl	190	52
5k	CH_3	Br	180	51
5l	CH_3	NO_2	183	50

Antimicrobial activities of compound (**5a-l**) :

The newly synthesized β-diketones have been screened for antibacterial activity against *Staphylococcus aureus* and *Klebsiella pneumoniae* and antifugal activity against *Aspergillus niger* and *Candida albicans* at concentration of 1000 μg by cup-plate method[33,34]. Ciprofloxin and Ciclopiroxolamine were used as standards for comparison of antibacterial and antifungal activities, respectively. The results indicate that these compounds were moderately active against various bacteria such as (*S. aureus, K. pneumoniae*) and fungi (*A. niger, C. albicans*). Compounds (**5b, 5d, 5f, 5h, 5j, 5l**) showed good activity against *S. aureus, K. pneumoniae* and compounds (**5b,**

Table 2. Antibacterial and antifugal activity of compounds (**5a-l**)

	Antibacterial activity (zone of inhibition in mm)		Antifungal activity (zone of inhibition in mm)	
Compd.	*S. aureus*	*K. pneumoniae*	*A. niger*	*C. albicans*
5a	12	09	17	15
5b	23	25	23	24
5c	12	09	16	18
5d	23	22	23	26
5e	12	09	14	13
5f	22	24	21	25
5g	11	09	17	18
5h	23	25	22	26
5i	13	09	14	18
5j	23	26	21	26
5k	12	08	16	18
5l	23	25	23	26
Std.	24	26	22	24

5d, 5f, 5h, 5j, 5l) showed good activity against *A. niger* and *C. albicans*. The results of antibacterial and antifungal studies are given in Table 2.

Experimental

All the melting points were determined in open glass capillary tubes and are uncorrected. All the compounds were subjected to elemental analysis (CHN) by Perkin-Elmer 2400 CHN analyser. The IR spectra (ν_{max} in cm^{-1}) were recorded on FT IR model SHIMADZU-8400S grating infrared spectrophotometer in KBr pellets. ^1H NMR spectra were measured on JEOL-AL 300 spectrophotometer at 300 MHz and ^{13}C NMR spectra were recorded at 75.45 MHz using TMS as an internal standard (chemical shift in δ ppm), $CDCl_3$ was taken as a solvent. The IR and ^1H NMR were recorded at Department of Chemistry, University of Rajasthan, Jaipur. The purity of newly synthesized compounds were checked by TLC using silica gel G as adsorbent and visualization was accomplished by UV light or iodine.

General method for the synthesis of substituted 1-phenyl-4-(pyrazol-1-yl)-butane-1,3-dione (**5**) : It was synthesized by following procedure, which involves three steps.

(i) Synthesis of pyrazole-1-acetic acid (**2**) :

Pyrazole (0.01 *M*) with equivalent quantity of CH_3ONa in methanol were stirred at room temperature on a magnetic stirrer for half an hour, until a creamy mass was obtained. Now α-chloroacetic acid (0.02 *M*) was added to the reaction mixture in small portions and the reaction mass was stirred continuously for four hours at 60 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was cooled and solvent was removed under reduced pressure. Now the compound was extracted with chloroform : ethylacetate (1 : 1). It was crystallized from chloroform (m.p. 110 °C, yield 60%).

(ii) Synthesis of pyrazole-1-acetyl chloride (**3**) :

Pyrazole-1-acetic acid (0.01 *M*) was taken in a two necked round bottom flask fitted with a dropping funnel and condenser. Thionyl chloride (0.01 *M*) was added dropwise in order to dissolve the solid and it was refluxed for three hours. After completion of the reaction, reaction mixture was cooled and excess of thionyl chloride was distilled off under reduced pressure. The compound was crystallized from chloroform (m.p. 125 °C, yield 56%).

(iii) Synthesis of 1-phenyl-4-(pyrazol-1-yl)-butane-1,3-dione (**5a**) :

A mixture of sodium methoxide (0.01 *M*) and acetophenone derivative (0.01 *M*) was stirred for one hour on a magnetic stirrer at 50 °C, to obtain the sodium salt of acetophenone. Pyrazole-1-acetyl chloride (**3**) (0.01 *M*) was

added in small portions and dry toluene (15 ml) was added as a solvent to effect proper stirring of the reaction mass. The reaction mixture was refluxed at 80 °C for about twenty hours. After completion of the reaction, the reaction mixture was kept overnight in refrigerator and toluene was removed under reduced pressure. The reaction mixture was then extracted with chloroform and washed several times with water. The crude product was recrystallized from absolute alcohol. Compound **5a** obtained as crystalline solid. Purity of β-diketone was checked through TLC using benzene : ethanol : ammonia (7 : 2 : 1).

Spectral data :

1-Phenyl-4-(pyrazol-1-yl)-butane-1,3-dione (**5a**) :

Yield 56%, m.p. 168 °C; Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.26; N, 12.28. Found : C, 68.41; H, 5.25; N, 12.27; IR (KBr) ν_{max} (cm^{-1}) : 3050, 2890, 1740, 1690, 1585, 1494, 1449; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.50–8.16 (8H, m, Ar-H), 6.47 (2H, s, $>CH_2$), 4.89 (2H, s, $-NCH_2$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 65.7 (NCH_2), 47.2 (CH_2), 105–141 (Ar-C), 196.9, 192.0 (C=O); MS : *m/z* 228 $[M]^+$.

1-(4-Methylphenyl)-4-(pyrazol-1-yl)-butane-1,3-dione (**5b**) :

Yield 51%, m.p. 175 °C; Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.78; N, 11.57. Found : C, 69.40; H, 5.76; N, 11.56; IR (KBr) ν_{max} (cm^{-1}) : 3045, 2895, 1740, 1690, 1580, 1495, 1475, 1375; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.62–8.13 (7H, m, Ar-H), 6.31 (2H, s, $>CH_2$), 5.03 (2H, s, $-NCH_2$), 2.12 (3H, s, $-CH_3$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 20.9 (CH_3), 69.2 (NCH_2), 49.5 (CH_2), 108–135 (Ar-C), 196.9, 191.9 (C=O); MS : *m/z* 242 $[M]^+$.

1-(4-Methoxyphenyl)-4-(pyrazol-1-yl)-butane-1,3-dione (**5c**) :

Yield 58%, m.p. 181 °C; Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.42; N, 10.85. Found : C, 65.10; H, 5.41; N, 10.83; IR (KBr) ν_{max} (cm^{-1}) : 3025, 2885, 1740, 1685, 1580, 1490, 1450, 1058, 1248; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.87–7.91 (7H, m, Ar-H), 6.32 (2H, s, $>CH_2$), 4.70 (2H, s, $-NCH_2$), 3.70 (3H, s, $-OCH_3$); ^{13}C NMR (75.45 MHz, $CDCl_3$) : δ 68.2 (NCH_2), 56.5 (OCH_3), 48.1 (CH_2), 106–139 (Ar-C), 198.5, 194.0 (C=O); MS : *m/z* 258 $[M]^+$.

1-(4-Chlorophenyl)-4-(pyrazol-1-yl)-butane-1,3-dione (**5d**) :

Yield 49%, m.p. 183 °C; Anal. Calcd. for $C_{13}H_{11}N_2O_2Cl$: C, 59.42; H, 4.19; N, 10.66. Found : C, 59.42; H, 4.18; N, 10.65; IR (KBr) ν_{max} (cm^{-1}) : 3035, 2880, 1740, 1692, 1590, 1492, 1454, 600; ^1H NMR (300 MHz, $CDCl_3$) δ : 7.10–7.91 (7H, m, Ar-H), 6.41 (2H, s, $>CH_2$), 4.95 (2H, s, $-NCH_2$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 68.9 ($-NCH_2$), 49.2 (CH_2), 104–145 (Ar-C), 196.2, 191.1 (C=O); MS : *m/z* 262 $[M]^+$.

1-(4-Bromophenyl)-4-(pyrazol-1-yl)-butane-1,3-dione (**5e**) :

Yield 54%, m.p. 180 °C; Anal. Calcd. for $C_{13}H_{11}N_2O_2Br$: C, 50.98; H, 3.59; N, 9.15. Found : C, 50.96; H, 3.58; N, 9.14; IR (KBr) ν_{max} (cm^{-1}) : 3040, 2905, 1740, 1685, 1590, 1490, 1454, 500; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.58–7.86 (7H, m, Ar-H), 6.50 (2H, s, $>CH_2$), 4.85 (2H, s, $-NCH_2$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 50.1 (CH_2), 70.2 ($-NCH_2$), 102–105 (Ar-C), 194.9, 190.9 (C=O); MS : *m/z* 306 $[M]^+$.

1-(4-Nitrophenyl)-4-(pyrazol-1-yl)-butane-1,3-dione (**5f**) :

Yield 50%, m.p. 165 °C; Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.02; N, 15.38. Found : C, 57.12; H, 4.01; N, 15.36; IR (KBr) ν_{max} (cm^{-1}) : 3050, 2915, 1740, 1700, 1580, 1494, 1450; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.95–8.30 (7H, m, Ar-H), 6.50 (2H, s, $>CH_2$), 4.82 (2H, s, $-NCH_2$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 47.8 (CH_2), 65.8 (NCH_2), 105–152.8 (Ar-C), 192, 196.5 (C=O); MS : *m/z* 273 $[M]^+$.

1-Phenyl-4-(3-methylpyrazol-1-yl)-butane-1,3-dione (**5g**) :

Yield 54%, m.p. 170 °C; Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.78; N, 11.57. Found : C, 69.41; H, 5.75; N, 11.54; IR (KBr) ν_{max} (cm^{-1}) : 3025, 2885, 1735, 1690, 1580, 1480, 1454, 1345; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.54–7.89 (7H, m, Ar-H), 6.39 (2H, s, $>CH_2$), 4.78 (2H, s, $-NCH_2$), 2.70 (C-CH_3); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 13.8 (CH_3), 48.5 (CH_2), 66.1 (NCH_2), 104–139 (Ar-C), 190.0, 192.5 (C=O); MS : *m/z* 242 $[M]^+$.

1-(4-Methylphenyl)-4-(3-methylpyrazol-1-yl)-butane-1,3-dione (**5h**) :

Yield 50%, m.p. 165 °C; Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.31; H, 6.25; N, 10.93. Found : C, 70.29; H, 6.23; N, 10.91; IR (KBr) ν_{max} (cm^{-1}) : 3048, 2898, 1740, 1690, 1580, 1478, 1454, 1370; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.58–7.48 (6H, m, Ar-H), 6.48 (2H, s, $>CH_2$), 4.84 (2H, s, $-NCH_2$), 2.79 (3H, s, CH_3), 2.15 (3H, s, CH_3); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 13.8 (CH_3), 20.9 (CH_3), 65.2 (NCH_2), 48.5 (CH_2), 108–149.5 (Ar-C), 190.1, 193.5 (C=O); MS : *m/z* 256 $[M]^+$.

1-(4-Methoxyphenyl)-4-(3-methylpyrazol-1-yl)-butane-1,3-dione (**5i**) :

Yield 55%, m.p. 175 °C; Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.17; H, 5.88; N, 10.29. Found : C, 66.15; H, 5.87; N, 10.28; IR (KBr) ν_{max} (cm^{-1}) : 3025, 2895, 1720, 1685, 1585, 1472, 1454, 1375, 1248, 1058; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.65–7.75 (6H, m, Ar-H), 6.42 (2H, s, $>CH_2$), 4.84 (2H, s, $-NCH_2$), 2.75 (3H, s, CH_3), 3.75 (3H, s, $-OCH_3$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 14.8 (CH_3), 56.2 (OCH_3), 66.4 (NCH_2), 47.9 (CH_2), 106–150 (Ar-C), 191.9, 194.5 (C=O); MS : *m/z* 272 $[M]^+$.

1-(4-Chlorophenyl)-4-(3-methylpyrazol-1-yl)-butane-1,3-dione (**5j**) :

Yield 52%, m.p. 190 °C; Anal. Calcd. for $C_{14}H_{13}N_2O_2Cl$: C, 60.75; H, 4.70; N, 10.12. Found : C, 60.73; H, 4.69; N, 10.11; IR (KBr) ν_{max} (cm^{-1}) : 3087, 2885, 1725, 1692, 1590, 1475, 1454, 1365, 600; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.80–7.87 (6H, m, Ar-H), 6.38 (2H, s, $>CH_2$), 4.85 (2H, s, $-NCH_2$), 2.70 (3H, s, CH_3); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 13.9 (CH_3), 66.8 (NCH_2), 49.8 (CH_2), 105.7–149 (Ar-C), 190.8, 194.0 (C=O); MS : *m/z* 276 $[M]^+$.

1-(4-Bromophenyl)-4-(3-methylpyrazol-1-yl)-butane-1,3-dione (**5k**) :

Yield 51%, m.p. 180 °C; Anal. Calcd. for $C_{14}H_{13}N_2O_2Br$: C, 52.50; H, 4.06; N, 8.75. Found : C, 52.49; H, 4.05; N, 8.73; IR (KBr) ν_{max} (cm^{-1}) : 3067, 2875, 1740, 1685, 1585, 1450, 1415, 1350, 500; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.89–7.92 (6H, m, Ar-H), 6.41 (2H, s, $>CH_2$), 4.90 (2H, s, $-NCH_2$), 2.72 (3H, s, CH_3); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 13.8 (CH_3), 69.8 (NCH_2), 50.40 (CH_2), 105–141 (Ar-C), 190.0, 194.6 (C=O); MS : *m/z* 320 $[M]^+$.

1-(4-Nitrophenyl)-4-(3-methylpyrazol-1-yl)-butane-1,3-dione (**5l**) :

Yield 50%, m.p. 183 °C; Anal. Calcd. for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.53; N, 14.63. Found : C, 58.51; H, 4.51; N, 14.62; IR (KBr) ν_{max} (cm^{-1}) : 3060, 2870, 1735, 1700, 1595, 1470, 1455, 1425, 1360; ^1H NMR (300 MHz, $CDCl_3$) δ : 6.52–7.89 (6H, m, Ar-H), 4.88 (2H, s, $-NCH_2$), 6.48 (2H, s, $>CH_2$), 2.76 (3H, s, CH_3); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ : 13.8 (CH_3), 69.6 (NCH_2), 50.8 (CH_2), 105–141 (Ar-C), 191, 194.5 (C=O); MS : *m/z* 287 $[M]^+$.

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References

1. T. Eicher and S. Hauptmann, "The Chemistry of Heterocycles : Structure, Reactions, Syntheses, and Applications", Wiley-VCH, ISBN 3527307206, 2003, 2nd ed.
2. P. D. Sauzem, P. Machado, M. A. Rubin, G. da. S. Sant'Anna, H. B. Faber, A. H. de Souza, C. F. Mello, P. Beck, R. A. Burrow, H. G. Bonacorso, N. Zanatta and M. A. P. Martins, *Eur. J. Med. Chem.,* 2008, **43**, 1237.
3. M. Amir and K. Shikha, *Eur. J. Med. Chem.*, 2004, **39**, 535.
4. E. Palaska, G. Sahin, P. Kelicen, N. T. Durlu and G. Altinok, *Farmaco,* 2002, **57**, 101.
5. E. Palaska, G. Sahin, P. Kelicen, R. Demirdamar and G. Altinok, *Arzneim.-Forsch./Drug Res.,* 2001, **51**, 478; *Chem. Abstr.*, 2001, **135**, 326954a.
6. A. A. Bekhit, H. M. A. Ashour, Y. S. Abdel Ghany, A. A. Bekhit and A. Baraka, *Eur. J. Med. Chem.*, 2008, **43**, 456.
7. A. Padmaja, T. Payani, G. Dinneswara Reddy and V. Padmavathi, *Eur. J. Med. Chem.,* 2009, **44**, 4557.
8. (a) R. V. Ragavan, V. Vijayakumar and N. S. Kumari, *Eur. J. Med. Chem.*, 2010 , **45**, 1173; (b) W. A. El-Sayed, E. M. Flefel and E. M. H. Morsy, *Der Pharma Chemica*, 2012, **4**, 23.
9. (a) S. M. Riyadh, T. A. Farghaly, M. A. Abdallah, M. M. Abdalla and M. R. Abd El-Aziz, *Eur. J. Med. Chem.,* 2010, **45**, 1042; (b) M. A. El-Borai, H. F. Rizk, M. F. Abd-Aal and I. Y. El-Deeb, *Eur. J. Med. Chem.,* 2012, **48**, 92; (c) I. Vujasinovic, A. Paravic-Radicevic, K. Mlinaric-Majerski, K. Brajsa and B. Bertosa, *Bioorg. Med. Chem.,* 2012, **20**, 2101.
10. X. D. Yang, *J. Chem. Res.,* 2008, **9**, 489.

11. A. E. Rashad, M. I. Hegab, R. E. Abdel-Megeid, N. Fathalla and F. M. E. Abdel-Megeid, *Eur. J. Med. Chem.*, 2009, **44**, 3285.
12. E. Elzein, R. Kalla, X. Li, T. Perry, E. Parkhill, V. Palle, V. Varkhedkar, A. Gimbel, D. Zeng, D. Lustig, D. Leung and J. Zablocki, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 302.
13. W. L. John, R. M. Patera, M. J. Plummer, B. P. Halling and D. A. Yuhas, *Pest. Sci.*, 1994, **42,** 29.
14. M. J. Genin, C. Biles, B. J. Keiser, S. M. Poppe, S. M. Swaney, W. G. Tarpley, Y. Yagi and D. L. Romero, *J. Med. Chem.*, 2000, **43**, 1034.
15. V. A. Chornous, M. K. Bratenko, M. V. Vovk and I. I. Sidorchuk, *Pharm. Chem. J.,* 2001, **35**, 203.
16. H. E. Skipper, R. K. Robins J. R. Thomson, C. C. Cheng, R. W. Brockman and F. M. Schabel, *Cancer Res.*, 1957, **17**, 579.
17. H. E. Skipper, R. K. Robins and J. R. Thomson, *Proc. Soc. Expt. Biol. Med.*, 1955, **89**, 594.
18. H. M. Egg-Enweiler and V. Eiermann, *Ger. Offen, Chem. Abstr.*, 2002, **137**, 47210
19. C. Pettinari, F. Caruso, N. Zaffaroni, R. Villa, F. Marchetti, R. Pettinari and C. Phillips, *J. Inorg. Biochem.,* 2006, **100**, 58.
20. D. Bebbington, J. D. Charrier, R. Davies, S. Eveitt, D. Kay, R. Knegtal and S. Patel, *Chem. Abstr.*, 2002, **137**, 47221.
21. C. Cativiela, J. L. Serrano and M. M. Zurbano, *J. Org. Chem.*, 1995, **60**, 3074.
22. S. Surgiuro, S. Ohno, O. Ohtani, K. Izuni, T. Kitamikado, H. Asai, K. Kato, M. Hori and H. Fujimura, *J. Med. Chem.,* 1977, **20**, 18.
23. R. Unny, P. Joshi, M. P. Dobhal and Y. C. Joshi, *Heterocyclic Commun.*, 2003, **9**, 171.
24. J. Bhagwan, Y. C. Joshi, R. P. Tyagi, B. C. Joshi and H. N. Mangal, *J. Inst. Chem. (India)*, 1983, **55**, 58.
25. M. Padwad and V. N. Ingle, *J. Indian Chem. Soc.*, 1991, **76**, 161.
26. R. R. Gupta and R. K. Gautam, *Pharmazie*, 1985, **40**, 203.
27. S. Nigam, Y. C. Joshi and P. Joshi, *Heterocyclic Commun.*, 2003, **9**, 405.
28. A. Nagpal, R. Unny, P. Joshi and Y. C. Joshi, *Heterocyclic Commun.,* 2001, **7**, 589.
29. B. S. Patro, S. Rele, G. J. Chintalwar, S. Chattopadhyay, S. Adhikari and T. Mukherjee, *Chembiochem.*, 2002, **3**, 364.
30. K. Rehse and R. Bierifait, *Arch. Pharma. (Weinneim)*, 1984, **317**, 385.
31. M. Hirose, K. Ozaki, K. Takabo, S. Fukushima, T. Shiraj and N. Ito, *Carcinogensis*, 1991, **12,** 1917.
32. K. Takaba, M. Hirqse, Y. Yashida, J. Kimura and N. Ito, *Cancer Lett.*, 1997, **39**, 113.
33. A. R. Sundane, K. Rudresh, N. D. Satynarayan and S. P. Hiremath, *Indian J. Pharm. Sci.*, 1989, **60**, 379.
34. K. N. Giand, R. N. Dar, B. M. Chopra and R. N. Kaul, *Indian J. Pharm. Sci.*, 1965, **27**, 141.