Print ISSN: 0976-2876 Online ISSN: 2250-0138

Available online at: http://www.ijsr.in

INDIAN JOURNAL OF SCIENTIFIC RESEARCH

DOI:10.32606/IJSR.V13.I1.00012

Received: 02-03-2022 Accepted: 06-06-2022 Publication: 31-08-2022

Indian J.Sci.Res. 13 (1): 95-99, 2022 Original Research Article

SYNTHESIS OF CURCUMIN-PYRAZOLE ANALOGUES FROM SUBSTITUTED AROMATIC HYDRAZIDES BY GREEN PROTOCOL

MAHESH G. SHIOORKAR[a], MADHAV J. HEBADE[b] AND OMPRAKASH S. CHAVAN[c1]

[a]P.G. Department of Chemistry, Vivekanand College, Auranagabad, Maharashtra, India

[bc]P.G. Department of Chemistry, Badrinarayan Barwale College, Jalna, Maharashtra, India

ABSTRACT

Here we reported, primary, we synthesized aromatic hydrazide in lab and secondary, same synthesized aromatic hydrazide condensed with curcumin in presence of alum as a green catalyst, in small amount of water, as a green solvent, and under microwave irradiation as a green technique to produce better results w. r. t. yield, purity and time.

KEYWORDS: Curcumin Analogue, Aromatic Hydrazide, Alum, Water, MWI, Green Technique

Attempted have been made for synthesis of Curcumin-pyrazole analogues from substituted hydrazide condensation with 1,3-dicarbonyl moiety of Curcumin. Successful synthesis was achieved by using green methodology. Alum is naturally occurring substance consisting spectacular catalytic properties, and reports found (Pal et al., 2013) (Karimi and Bayat, 2016) (Li *et al.*, 2011). Few methods have been found in literature for the synthesis of Curcumin from hydrazide like reflux of Curcumin with substituted phenyl hydrazide (Ahsan *et al.*, 2013) in glacial acetic acid reflux for about 12-18 hours to obtained product. Another method reported by Sahu *et. al.*(2012) consist similar experimental procedure to that of previous one, refluxed with acetic acid. Longer reaction time and use of glacial acetic acid could be referred as drawbacks of these reactions.

EXPERIMENTAL

General procedure for Synthesis of aromatic hydrazide

Acid hydrazides were synthesized by using Yar *et. al.*(2007) method. Appropriate aromatic carboxylic acid (1 eq.) was added to absolute ethanol (10 eq.) and to this Conc. Sulphuric acid (3-4 ml) was added with stirring. Reaction mixture was refluxed for appropriate time (4-6 hours). On cooling poured to ice cold water and neutralized carefully by saturated solution of sodium bicarbonate, thus obtained oily layer separated with extraction with diethyl ether followed by evaporation of ether under reduced pressure. All products were used further without distillation.

General procedure for Synthesis of Curcumin pyrazole from Aromatic hydrazide

Curcumin (1mmol; 1 eq.) was taken in 10 ml of 10% of Alum in water (*w/v*) to this substituted hydrazide (1.5 mmol; 1.5 eq.) added in one portion and stirred for few minutes for homogenous mixing. Reaction contains were irradiate in Microwave oven at 600 Watt power for appropriate time. Resting time was set for 10 seconds after every 30 seconds of successive irradiation. Progress of reaction was monitor by TLC check (DCM: MeOH; 3:7), on completion of reaction allowed reaction contained to attained room temperature and filter. Thus obtained crude product was washing several times with water and finally recrystallized from hot alcohol to afford pure product.

RESULTS AND DISCUSSION

To improve yield of reaction and introduce green concern with respect to synthesis of curcumin-pyrazole reaction, efforts have been made and summarized as follows. Reaction was process in two steps, first to obtained substituted hydrazide from easily available and cheap aromatic carboxylic acid and second step was cyclocondensation of hydrazide and curcumin to produce desire product as depicted in Scheme 1.

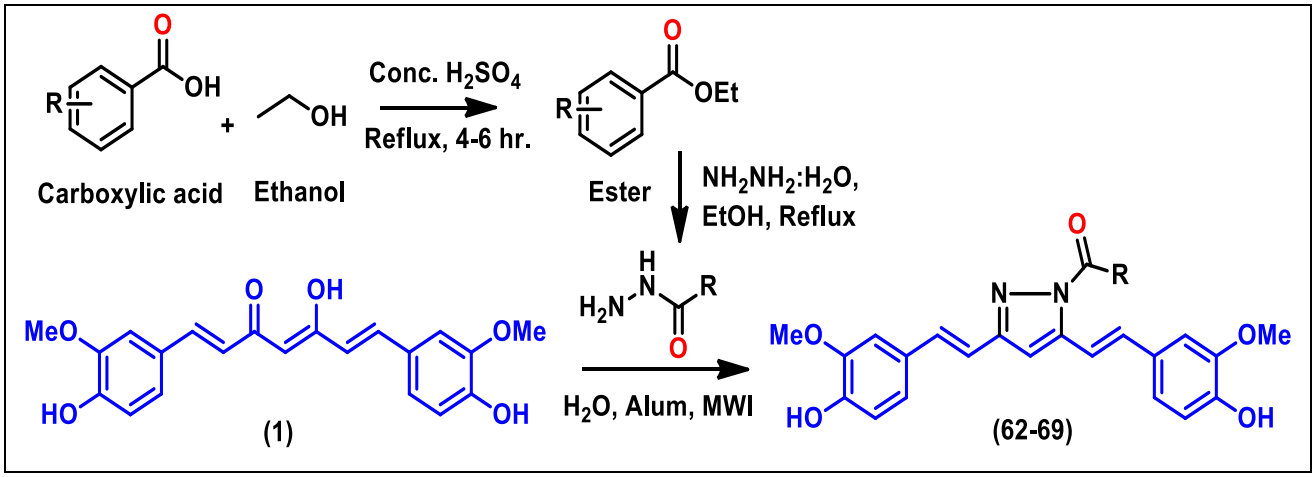
Model reaction strategy was employed to developed novel methodology for the synthesis of Curcumin-pyrazole. Curcumin and phenyl hydrazide were taken as fixed reactant to optimized reaction conditions with respect to solvent, catalyst and temperature. Stoichiometry of reaction were fixed to Curcumin 1 equivalent and phenyl hydrazide 1.5 equivalent to ensured all curcumin molecules get chance to convert into product. For fair comparison conventional

[1]Corresponding author

as well as non-conventional method was carried out for model reaction. During method development focus was kept on green concern and analogues catalyst/solvent pairs chosen as shown in table 1.

Satisfactory result were obtained when used alcohol and water as solvent with individual or as a mixture with either acetic acid or alum. Curcumin pyrazole condensation well established with glacial acetic acid, 10% potassium alum sulphate exhibits *p*H range 3-4, which found good replacement of acetic acid.

Scheme 1: Synthesis of Curcumin pyrazole from condensation reaction of Curcumin with substituted hydrazide in presence of water and alum as green solvent and catalyst



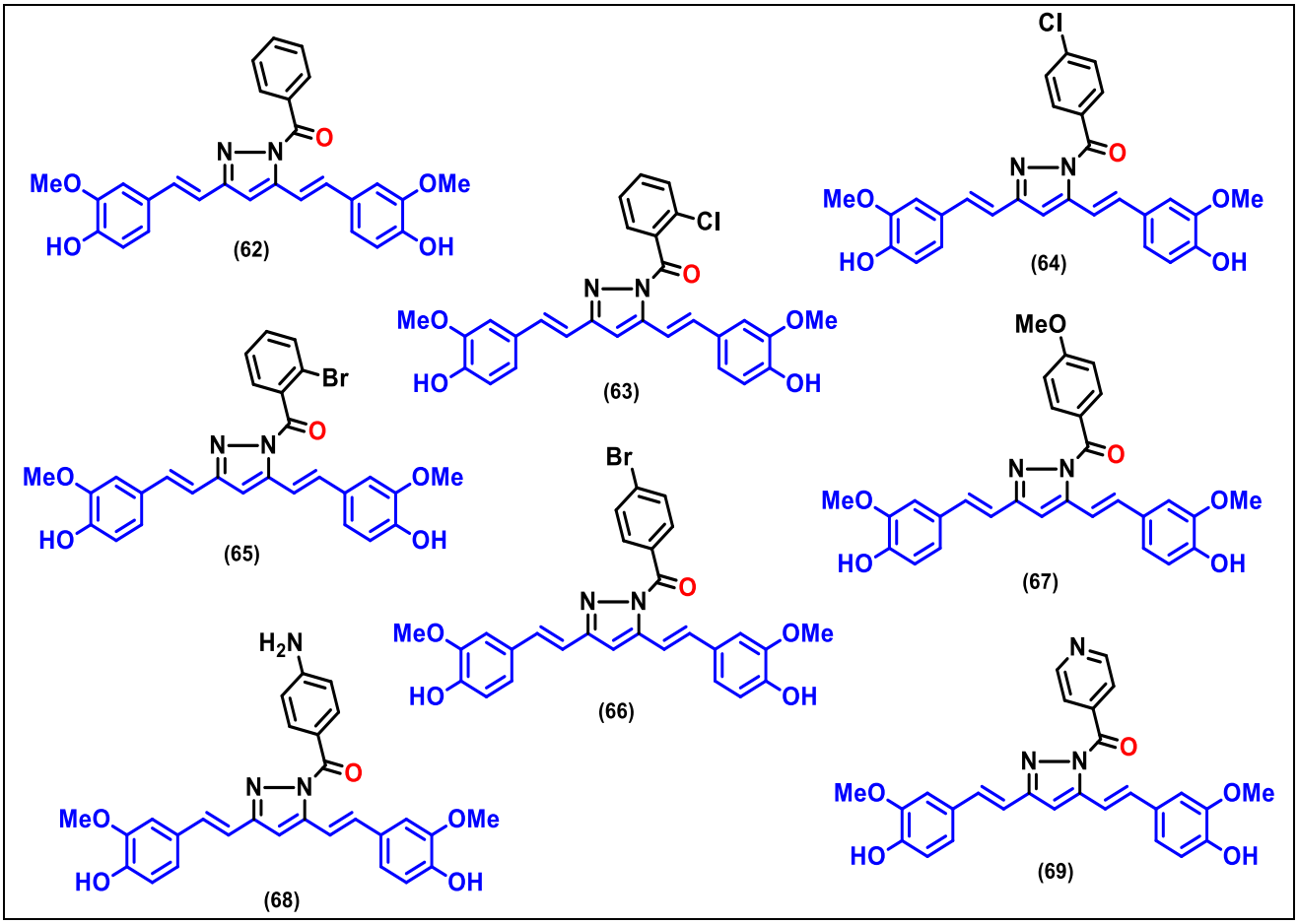


Figure 1: Structures of Curcumin pyrazole analogues

Table 1: Optimization of solvent for synthesis of (62) and with respect to yield

Entry	Solvent/ catalyst	Conventional method	Yield[a] of products	Non-conventional MWI method	Yield[a] of products
1	EtOH/AcOH	Reflux,4 hours	64%	600 Watt, 120 Sec.	72%
2	EtOH/Alum	Reflux,4 hours	57%	600 Watt, 120 Sec.	61%
3	EtOH:H_2O/ AcOH	Reflux,4 hours	43%	600 Watt, 120 Sec.	70%
4	EtOH:H_2O/Alum	Reflux,4 hours	70%	600 Watt, 120 Sec.	79%
5	H_2O/AcOH	Reflux,4 hours	53%	600 Watt, 120 Sec.	54%
6	H_2O/Alum	Reflux,4 hours	62%	600 Watt, 120 Sec.	90%
7	PEG-400/ AcOH	Reflux,4 hours	46%	600 Watt, 120 Sec.	56%
8	PEG-400/ Alum	Reflux,4 hours	51%	600 Watt, 120 Sec.	42%
9	Acetonitrile/ AcOH	Reflux,4hours	37%	600 Watt, 120 Sec.	Trace
10	Acetonitrile/ Alum	Reflux,4 hours	20%	600 Watt, 120 Sec.	Trace

[a]Isolated yield; [b]MWI 600W; *TLC Check

Alcohol, water, Polyethylene glycol-400 (PEG-400) was tried with catalytic amount of acetic acid or potassium aluminum sulphate. Results obtained (Table 1) clearly indicates that ethanol: acetic acid are good solvent: catalyst pair and water: Alum is newly immerging pair, among these two second one is more favorable due to environment-friendly nature. Handling 10% alum is less nasty than glacial acetic acid. Water: alum pair found more productive compared to Ethanol and acetic acid combination. Introduction of MWI for transformation of Curcumin to curcumin-pyrazole offers excellent result. Microwave has capacity to transfer huge amount of energy to reacting molecules within no time, this huge energy helps to cross energy barriers and expeditious products obtained. Water: alum pair when introduced with non-conventional method offers 90% yield of product (Table 1; Entry 6).

Stoichiometric ratio of Alum in water optimized by performing series of reactions, as depicted in table 2. Various proportion of Potash alum was prepared by weight by volume like 2%, 5%, 10%, 15% and 20%. To minimize error all solutions were prepared for 100ml of distilled water just prior to use for reaction. All combinations introduced for non-conventional microwave method and none of these except table 2; Entry 3 tried with conventional method. Considerable results obtained from 5% to 20% alum.

Table 2: Optimization of solvent/catalyst ratio and effective MWI power with respect to yield of product

Entry	H_2O/Alum (vol./Wt.)	Time in Sec.	Yield[a] of products
1	2%Alum	600 Watt, 120 Sec.	Staring recover*
2	5%Alum	600 Watt, 120 Sec.	45%
3	10%Alum	600 Watt, 120 Sec.	90%
4	15%Alum	600 Watt, 120 Sec.	91%
5	20%Alum	600 Watt, 120 Sec.	94%
6	10%Alum	300 Watt, 120 Sec.	37%
7	10%Alum	400 Watt, 120 Sec.	61%
8	10%Alum	800 Watt, 120 Sec.	Black sticky mass

[a]Isolated yield; *TLC Check

During gradual increment of 10% to 15% and further 20% of alum no significant elevation or depression of yield of product has been observed. Although, 10% of catalyst yield 90% productivity and further increases in catalytic amount did not found atom economic one this stoichiometric proportion with non-conventional MWI used further for derivatisation.

Table 3: Optimization of solvent/catalyst ratio and effective MWI power with respect to yield of product

Entry	Product No.	Yield[a] (in %)	Melting point (Balaji *et al.*, 2015)
1	(62)	90%	112°C
2	(63)	88%	168°C
3	(64)	92%	163°C
4	(65)	94%	283°C
5	(66)	89%	128°C
6	(67)	90%	217°C
7	(68)	67%	106°C
8	(69)	83%	123°C

[a]Isolated yield

Effect of substituent on yield of product was study using various substituted phenyl hydrazide reaction with curcumin and results depicted in table 3. Curcumin pyrazole offers better yield with Chloro- and Bromo-substituted phenyl hydrazide than 4-amino substituted phenyl hydrazide. These could be related with polar and basic nature of amine group which allowed product to loss during workup. To investigate this some changes has been made to workup procedure for product 69. After cooling of reaction contains neutralized by aq. $NaHCO_3$ and extracted with ethyl acetate, on evaporation at reduced pressure after treating with anhydrous Na_2SO_4 to afford product and yield of product elevated to 82% (formally it was, 67%) (Table 2; Entry 7).

In conclusion, describe method has contain significant green concern. It does contain water as universally accepted and unique green solvent. Replacement of hazardous glacial acid, which was necessary in previously reported methods, is considerable advantage. Potassium aluminum sulphate (Potash Alum) immerged as novel catalyst for curcumin-pyrazole synthesis. Use of non-conventional methods particularly MWI, made this procedure quick, within couple of minutes product has been obtained. Handling simplicity could be added to advantage of present method, easy workup procedure without nasty purification column chromatography techniques made describe method unique.

Spectral Analysis of Synthesized Compounds

(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)(phenyl)methanone (62):

IR: (KBr) cm^{-1}: 3349 (OH), 3133 (NH), 1737 (C=O), 1588 (C=N), 1369 (C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.92 (6H, s, OCH_3), 6.25 (1H, s, H-4), 6.84 (2H, d, H2,6), 6.86 (2H, d, H-1,7), 6.90–7.94 (11H, m, ArH), 9.89 (2H, broad, OH); ^{13}C NMR (75 MHz, DMSO-d_6) ppm: 55.57 (-OCH_3), 109.8 (C-4),111.8 (ArC), 116.8-116.9 (ArC and C-1,7), 128.3 (ArC), 134.6-134.7 (ArC and C-2,4), 147 (ArC-4,4'), 149.1 (ArC3,3'), 161.3 (CO).

(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)(2-chlorophenyl)methanone (63): IR: (KBr) cm^{-1}: 3346 (OH), 3136 (NH), 1730 (C=O), 1580 (C=N), 1355 (C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.90 (6H, s, OCH_3), 6.29 (1H, s, H-4), 6.82 (2H, d, H2,6), 6.84 (2H, d, H-1,7), 7.06–7.17 (m, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) ppm:56.34 (-OCH_3), 107.9 (C-4), 112.8 (ArC), 115.6-116.3 (ArC and C-1,7), 129.3 (ArC),133.6-134.1 (ArC and C-2,4), 147 (ArC-4,4'), 149.1 (ArC-3,3'), 165.2 (CO)

(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)(4-chlorophenyl) methanone (64): IR: (KBr) cm^{-1}: 3421 (OH), 3149 (NH), 1730 (C=O), 1543 (C=N), 1384 (C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.87 (6H, s, OCH_3), 6.67 (1H, s, H-4), 6.74 (2H, d, H2,6), 6.87 (2H, d, H-1,7), 7.16–7.88 (m, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) ppm: 56.12 (OCH_3),107.9 (C-4),109.3 (ArC),111.3 (ArC), 116.2-116.8 (ArC and C-1,7), 128.3 (ArC), 134.6-134.7 (ArC and C-2,4), 147 (ArC-4,4'), 149.1 (ArC-3,3'), 165.8 (CO).

(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)(2-bromophenyl) methanone (65): IR: (KBr) cm^{-1}: 3410 (OH), 3121 (NH), 1712(C=O), 1597 (C=N), 1343(C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (6H, s, OCH_3), 6.44(1H, s, H-4), 6.34 (2H, d, H-2,6), 6.69 (2H, d, H-1,7),6.82–7.96 (m, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) ppm: 56.21 (OCH3), 110.3 (C-4), 111.6 (ArC), 115.5-116.1 (ArC and C-1,7), 128.4 (ArC), 134.2134.5 (ArC and C-2,4), 149 (ArC-4,4'), 150.7 (ArC-3,3'), 162.6 (CO).

(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)(4-bromophenyl) methanone (66): IR: (KBr) cm^{-1}: 3364 (OH), 3142 (NH), 1730 (C=O), 1589 (C=N), 1342 (C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.87 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.26 (1H, s, H4), 6.81 (2H, d, H-2,6), 6.85 (2H, d, H-1,7), 6.89–7.96 (m, ArH), 9; ^{13}C

NMR (75 MHz, DMSO-d_6) ppm: 56.2 (-OCH_3), 56.61 (-OCH_3), 110.3 (C-4), 111.4 (ArC), 116.2-116.7 (ArC and C-1,7), 128.3 (ArC), 134.2-134.5 (ArC and C-2,4), 148.2 (ArC-4,4'), 149.1 (ArC-3,3'), 162.6 (CO).

(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)(4-methoxyphenyl) methanone (67): IR: (KBr) cm^{-1}: 3379 (OH), 3145 (NH), 1742 (C=O), 1579 (C=N), 1365 (C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ δ 3.85 (3H, s, OCH_3),3.87 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.22 (1H, s, H-4), 6.81 (2H, d, H-2,6), 6.89 (2H, d, H-1,7), 6.97–7.23 (m, ArH); ^{13}CNMR (75 MHz, DMSO-d_6) ppm: 55.3 (-OCH_3), 55.4 (-OCH_3), 56.1 (-OCH_3), 109.4(C-4), 112.1 (ArC), 116.1-116.7 (ArC and C-1,7), 128.8 (ArC), 134.1-135.2 (ArC and C-2,4), 147 (ArC-4,4'), 149.3 (ArC-3,3'), 164.3 (CO).

(4-aminophenyl)(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1yl)methanone (68): IR: (KBr) cm^{-1}: 3349 (OH), 3244 (NH), 1731 (C=O), 1490 (C=N), 1355 (C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.87 (3H, s, OCH_3), 3.92 (3H, s, OCH_3) 6.52 (2H, d, ArH), 6.64 (1H, d, H-4), 6.93–6.99 (m, ArH), 7.75 (2H, d, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) ppm: 56.3 (-OCH_3), 56.7 (-OCH_3), 107.2(C-4), 109.4(ArC-2,2'), 114.8 (ArC3",5"), 116.2 (C-2), 116.7 and116.8 (C-1,7), 129.2 (ArC), 134.4 and134.9 (C-2,4), 149.3 (ArC-4,4'), 149.7 (ArC-3,3'), 165.1 (CO).

(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (69): IR: (KBr) cm^{-1}: 3433 (OH), 3110 (NH), 1757 (C=O), 1514 (C=N), 1344 (C–N). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.64 (1H, s, H4), 6.95–6.99 (4H, d, H-1,2,6,7), 7.09-7.13 (m, ArH), 7.93 (2H,d, Py), 8.83 (2H,d, Py); ^{13}C NMR (75 MHz, DMSO-d_6) ppm:56.8 (-OCH_3), 57.6 (-OCH_3), 107.3(C-4), 111.2 (ArC), 114.7 and115.2 (ArC and C-1,7), 126.7 (ArC), 133.1 and134.7 (ArC and C-2,4), 148.1 (ArC-4,4'), 148.3(ArC-3,3'), 166.4 (CO).

CONCLUSION

In brief, we concluded here that, for synthesis of various analogues of Curcumin-pyrazole from condensation reaction of Curcumin with substituted hydrazide in presence of water and alum as green solvent and catalyst under microwave irradiation method for good to better yield in very small amount of time reaction.

ACKNOWLEDGMENT

The authors are thankful to Principal and Management of Badrinarayan Barwale Senior College, Jalna-431213 for encouragement for this research work and providing all necessary laboratory facility.

REFERENCES

Ahsan M.J., Khalilullah H., Yasmin S., Jadhav S.S. and Govindasamy J., 2013. Synthesis, Characterisation, and in vitro anticancer activity of curcumin analogues bearing pyrazole/pyrimidine ring targeting EGFR tyrosin kinase, Bio Med Research International, Aricle ID 239354, 1-14.

Balaji S.N., Ahsan M.J., Jadhav S.S. and Trivedi V., 2015. Molecular modelling, synthesis, and antimalarial potentials of curcumin analogues containing heterocyclic ring, Arabian J. Chem. In press [http://dx.doi.org/10.1016/j.arabjc. 2015.04.011]

Karimi A.R. and Bayat F., 2016. Mono- and Bis-Pyrimido[1,2-a]benzimidazoles: Alum Catalyzed Regioselective Three- or Pseudo Five-Component Reaction of 2-Aminobenzimidazole with Aldehyde and Malononitrile, Letter in Org. Chem., **13**(10): 631-636.

Li W.L., Wu L.Q. and Yan F.L., 2011. Alum-catalyzed one-pot synthesis of dihydropyrano[3,2-b]chromenediones, **22**(11): 2202-2205.

Pal G., Paul S. and Das A.R., 2013. Alum-Catalyzed Synthesis of 3-(1H-Pyrrol-2-yl)-2H-chromen-2-ones: A Water–PEG 400 Binary Solvent Mediated, One-Pot, Three-Component Protocol, Synthesis, **45**(9): 1191-1200.

Sahu P.M., Sahu P.K., Gupta S.K., Thavaselvam D. and Agarwal D.D., 2012. Synthesis and evaluation of antimicrobial activity of 4H-pyrimido[2,1-b]benzothiazole, pyrazole and benzylidene derivatives of curcumin, Eur. J. of Med. Chem., **54**: 366-378.

Yar M.S., Siddiqui A.A. and Ali M.A., 2007. Synthesis and antituberculostic activity of Novel 1,3,4-Oxadiazole derivatives, J. Chin. Chem. Soc., **54**: 5-8.