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**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**Available online at: <http://www.iajps.com>**Research Article****SYNTHESIS AND *INVITRO* BIOLOGICAL ACTIVITIES OF
SOME NOVEL ACRYLOYL CHROMENE-4-ONE DERIVATIVES.****Sheth Chintan*, Prakasha Kaggere Jayaramu*, Rohini R Maralihalli^a**

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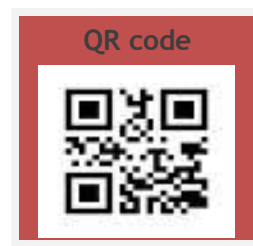
Abstract:

Some new acryloyl chromene-4-one derivatives were synthesized by Claisen-Schmidt condensation of 2-hydroxy acetophenone and benzaldehyde to form Chalcones which on further oxidative cyclization gives Flavone. Further on acetylation of Flavone, compound obtained was reacted with different substituted benzaldehyde to give acryloyl chromene-4-one derivatives. CN (1–10). The Characterization of newly synthesized compounds done on the basis of UV, IR, ¹HNMR, ¹³CNMR, Mass spectral data. All the synthesized compounds were evaluated for their anti-inflammatory and antitubercular activity.

Keywords: *chromene-4-one derivatives, Flavones, Spectral data, Anti-inflammatory activity, Antitubercular activity.*

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INTRODUCTION

Inflammation is a part of the complex biological response of the vascular tissues due to harmful stimuli. The signs of acute inflammation are pain, heat, redness and loss of functions. Acute inflammation is the initial response of the body to the harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood into the injured tissues. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the treatment of acute and chronic inflammation, pain and fever. Most of the NSAIDs that are available in the market are known to inhibit isoforms, a constitutive form COX-1 and an inducible form, COX-2 to offer therapeutic effect. However, long term clinical usage NSAIDs is associated with significant side effects of gastric lesions, bleeding and nephrotoxicity [1]. Therefore, the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area. Tuberculosis (TB) is one of the oldest and most pervasive diseases in history. According to alarming data from the World Health Organization (WHO), TB has spread to every corner of the globe. As much as one third of the world's population is currently infected and more than 5000 people die from TB every day. It is estimated that between 2002 and 2020, approximately 1000 million people will be newly infected, over 150 million people develop diseases and 36 million will die of TB if proper control measures are not established. The Direct Observed Treatment Short Course (DOTS) strategy constitutes the corner stone of the current protocol for control of TB. However, the three key drugs, isoniazide, pyrazinamide and rifampicin, used in the regimen are potentially hepatotoxic and may lead to drug-associated hepatitis.

The flavones (2-phenylchromones) are naturally occurring heterocyclic compound belonging to the flavanoid group and are widely distributed in vascular plants [2]. Their attraction as synthetic targets is due to wide range of biological activities exhibited by them. Their presence being a century old [3], isolation of new flavones [4] and new methods of synthesis continue till to date. The flavones derivatives are investigated and reported for leishmanicidal activity, oviposter stimulant

phytoalexins, anti-HIV, vasodilator, antiviral, anti-oxidants, bactericidal, anti-inflammatory, antimutagenics, antiallergic and anticancer [5]. Moreover, it is known that some flavones have a repelling property against some phytophagous insects[6-7].

MATERIALS AND METHODS

All the melting points were determined in a Thermo-nik melting point apparatus and are uncorrected. The IR spectra of the synthesized compounds was recorded on a Fourier Transform IR spectrometer (model Shimadzu 8700) in the range of 400-4000 cm^{-1} using KBr pellets and ^1H NMR spectra was recorded on Amx - 400 MHz NMR spectrometer using DMSO and the chemical shifts (δ) reported are in parts per million downfield using tetramethylsilane (TMS) as internal reference. ^{13}C -NMR spectra was recorded on Amx - 400 MHz NMR spectrometer using DMSO and the chemical shifts (δ) reported are in parts per million downfield using tetramethylsilane (TMS) as an internal reference. Mass spectrum was recorded on Mass spectrophotometer (model Shimadzu) by LC-MS 2010A. The purity of the compounds was checked by thin-layer chromatography on silica gel G plates of 0.5 mm thickness as stationary phase and combination of n-hexane: ethyl acetate in different ratios as mobile phase. The UV spectra of the synthesized compounds were recorded on UV-Visible spectrophotometer (model Shimadzu 1601) using methanol and the values of absorption maxima (λ_{max}) were reported in nm.

RESULTS AND DISCUSSION

Antitubercular Activity [8-9]:

All the synthesized compounds were screened for *in-vitro* antitubercular activity by Microplate Alamar Blue Assay(MABA) method using Indomethacin as standard. Compounds of CN series were tested for antitubercular activity at concentration of 100 $\mu\text{g}/\text{ml}$ to 0.8 $\mu\text{g}/\text{ml}$ against the *M. Tuberculosis* ATTS 27294. All the derivatives exhibited antitubercular activity at 100 $\mu\text{g}/\text{ml}$. The results are given in the following table 1.

Table 1: Antitubercular Activity

Sl. No	Compounds	100µg/ml	50µg/ml	25µg/ml	12.5µg/ml	6.25µg/ml	3.12µg/ml	1.6µg/ml	0.8µg/ml
1	CN 1	S	S	S	S	S	R	R	R
2	CN 2	S	S	S	R	R	R	R	R
3	CN 3	S	S	S	S	R	R	R	R
4	CN 4	S	R	R	R	R	R	R	R
5	CN 5	S	S	R	R	R	R	R	R
6	CN 6	S	S	R	R	R	R	R	R
7	CN 7	S	S	R	R	R	R	R	R
8	CN 8	S	R	R	R	R	R	R	R
9	CN 9	S	S	R	R	R	R	R	R
10	CN 10	S	R	R	R	R	R	R	R
Standard	Isoniazide	S	S	S	S	S	S	S	S

S-Sensitive

R-Resistant

Anti-inflammatory Activity [10]:

The anti-inflammatory activity of the synthesized compounds tested at 100 and 200 µg/ml for anti-inflammatory activity by Bovine serum albumin (BSA) method and Indomethacin was used as positive control. Moderate activity was exhibited, dose dependent activity was observed for CN 1, CN 6, CN 8 and CN 9 respectively. The results are demonstrated in table 2.

Table 2: Anti-inflammatory activity

Compound Code	% Inhibition	
	100 µg/ml	200µg/ml
CN 1	38	52
CN 2	60	50
CN 3	44	43
CN 4	33	27
CN 5	65	52
CN 6	49	51
CN 7	58	56
CN 8	32	59
CN 9	48	51
CN 10	34	44
Indomethacin	86	88

Synthesis of 1-(2-Hydroxy phenyl)-3-phenyl-propenone. (3)

Equimolar quantity (0.01 mol) of 2-hydroxyacetophenone (1) and benzaldehyde (2) (0.01 mol) were dissolved in ethanol with aqueous KOH

and stirred for 6 hours by magnetic stirrer. Kept overnight. The reaction mixture was diluted with water, acidified with 10 % HCl to give chalcone (3). The obtained compound was recrystallized from ethanol.

Synthesis of 2-phenyl-chromene-4-one. (4)

Chalcones (3) (0.01 mol) was suspended in DMSO and crystal of Iodine was added to it and refluxed for 2.5 hrs. Reaction mixture was diluted with water, the obtained solid product is washed with 20% sodium thiosulphate and crude flavones (4) obtained was recrystallized from ethanol.

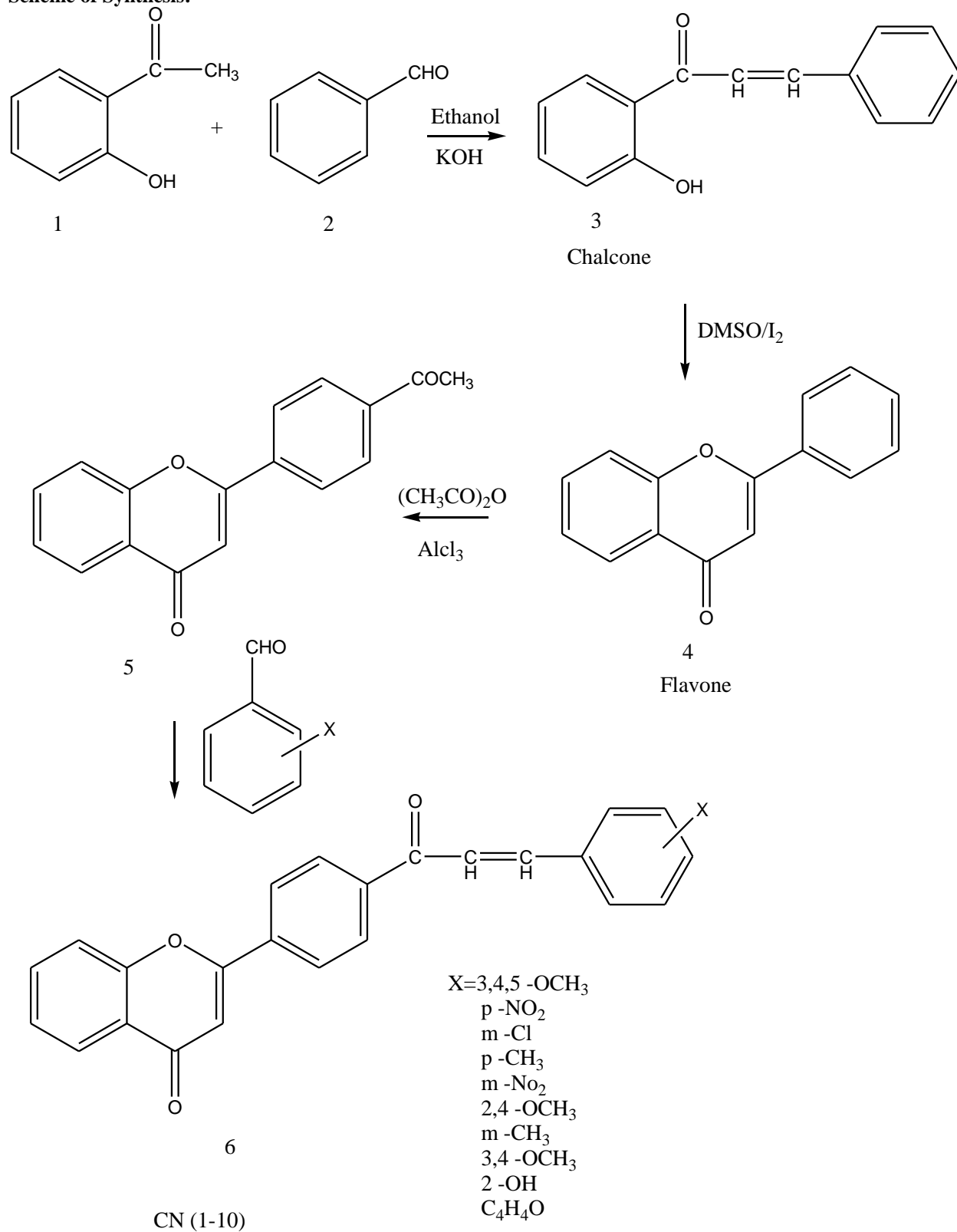
Synthesis of 2-(4-acetyl phenyl)-chromene-4-one. (5)

Equimolar quantity of Flavones (4) and acetic anhydride were mixed in round bottom flask with ethanol as a solvent. Anhydrous aluminium chloride was added as a catalyst in the reaction and refluxed for 3.5 hrs. The reaction mixture was cooled and poured in crushed ice. The obtained acetylated product (5) was filtered and recrystallized from ethanol.

Synthesis of 2-[4-(3-acryloyl)-phenyl]-chromene-4-one. CN (1 – 10)

Equimolar quantity of 2-(4-acetyl phenyl)-chromene-4-one (5) and different substituted benzaldehyde were dissolved in ethanol and aq. KOH and kept for stirring for 6 hrs and left overnight. The reaction mixture was diluted with water, and neutralized with 10 % HCl to obtain acryloyl phenyl chromene-4-one derivatives. The compounds obtained CN (1 – 10) were recrystallized from ethanol.

Scheme of Synthesis:



2-[4-[3-(3, 4, 5-trimethoxy-phenyl)-acryloyl]-phenyl]-chromene-4-one. (CN 1): Yield 48%; m.p.148°C; λ_{\max} =304nm; IR(KBr)cm⁻¹1676 (C=O), 1598 (C=C), 3064 (C-H), 1525 (C=C), 1266 (C-O str). ¹HNMR(DMSO) δ 8.1 (d, 1H), δ 7.8(m, 6H), δ 7.6(d, 1H, 1H), δ 7.5(s, 1H.), δ 3.9(t, 9H, OCH₃-). ¹³CNMR (DMSO) δ 180, 187 (C=O), δ 179 (CH), δ 152 (CH), δ 149 (C=O) δ 128, 127, 126, 124, 106 (aryl carbons).

2-[4-[3-(4-nitro-phenyl)-acryloyl]-phenyl]-chromene-4-one. (CN 2): Yield 56%; m.p.145°C; λ_{\max} =319nm; IR (KBr) cm⁻¹ 1691 (C=O), 1606 (C=C), 3066 (C-H), 1519 (C=C), 1292 (C-O str). ¹HNMR (DMSO) δ 8.1 (d, 1H), δ 7.7 (m, 8H) δ 7.6 (d, 1H), δ 7.1 (s, 1H). ¹³CNMR (DMSO) δ 192, 172, 149, 131, 128, 124, 123, δ 178 (C=O), δ 150 (C), δ 129 (C).

2-[4-[3-(3-chloro-phenyl)-acryloyl]-phenyl]-chromene-4-one. (CN 3): Yield 54%; m.p.151°C; λ_{\max} =317nm; IR (KBr) cm⁻¹ 1660 (C=O), 1593 (C=C), 3089 (C-H), 1525 (C=C), 1250 (C-Ostr). ¹HNMR (DMSO) δ 8.0(d, 1H), δ 7.6 (d, 1H), δ 7.51(s, 1H), δ 7.4 (m, 8H, Ar). ¹³CNMR (DMSO) δ 180 (C=O), δ 166, 134 (C=C δ 187, 132, 129, 127, 126, 124, 187 (aryl carbon)

2-[4-[3-(p-tolyl)-acryloyl]-phenyl]-chromene-4-one. (CN 4): Yield 62%; m.p.145°C; λ_{\max} =307nm; IR (KBr) cm⁻¹ 1677 (C=O), 1607 (C=C), 3062 (C-H), 1535 (C=C), 1262 (C-O str). ¹HNMR (DMSO) δ 7.95(d, 1H), δ 7.7(s, 1H), δ 7.5 (d, 1H), δ 7.4 (m, 8H), δ 2.5(s, 3H, CH₃). ¹³CNMR (DMSO) δ 188 (C), δ 187, 179, 149, 131, 128, 124, 123 (aryl carbon) δ 152, 129 (C=C).

2-[4-[3-(3-nitro-phenyl)-acryloyl]-phenyl]-chromene-4-one. (CN 5): Yield 58%; m.p.146°C, λ_{\max} =310nm; IR (KBr) cm⁻¹ 1689 (C=O), 1604 (C=C), 3070 (C-H), 1521 (C=C), 1294 (C-O str). ¹HNMR (DMSO) δ 8.5(d, 1H), δ 7.5 (s, 1H), δ 7.2 (m, 8H, Ar), δ 7.04 (d, 1H). ¹³CNMR (DMSO) δ 191, 155 (C=C), δ 148, 141, 140, 131, 128, 128, 127, 188, 177 (aryl carbon)

2-[4-[3-(2, 4-dimethoxy-phenyl)-acryloyl]-phenyl]-chromene-4-one. (CN 6): Yield 49%; m.p.150°C; λ_{\max} =311nm; IR (KBr) cm⁻¹1645 (C=O), 1591 (C=C), 3004 (C-H), 1519 (C=C), 1213 (C-O str).

2-[4-(3-m-tolyl)-acryloyl]-phenyl]-chromene-4-one (CN 7): Yield 60%; m.p.142°C, λ_{\max} =310nm; IR (KBr) cm⁻¹ 1663 (C=O), 1638 (C=C), 3032 (C-H), 1561 (C=C), 1260 (C-O).

2-[4-[3-(3, 4-dimethoxy-phenyl)-acryloyl]-phenyl]-chromene-4-one. (CN 8): Yield 54%; m.p.155°C;

λ_{\max} =319nm; IR (KBr) cm⁻¹ 1686 (C=O), 1609 (C=C), 3033 (C-H), 1562 (C=C), 1249 (C-O str).

2-[4-[3-(2-hydroxy-phenyl)-acryloyl]-phenyl]-chromene-4-one. (CN 9): Yield 60%; m.p.138°C; λ_{\max} =311nm; IR (KBr) cm⁻¹ 1663 (C=O), 1638 (C=C), 3032 (C-H), 1561 (C=C), 1280 (C-O str).

2-[4-[3-(4-furan-2-yl-phenyl)-acryloyl]-phenyl]-chromene-4-one. (CN 10): Yield 55%; m.p.142°C; λ_{\max} =320nm; IR (KBr) cm⁻¹1684 (C=O), 1609 (C=C), 3031 (C-H), 1512 (C=C), 1251 (C-Ostr).

Antitubercular Activity

The antitubercular activity of compounds was assessed against *M. Tuberculosis* using Microplate Alamar Blue Assay (MABA). Briefly, 200 μ l of sterile 96 wells plate was taken to minimize evaporation of medium in the test wells during incubation. The 96 wells plate received 100 μ l of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.8 μ g /ml. Plates were covered and sealed with parafilm and incubated at 37°C for five days. After this time, 25 μ l of freshly prepared 1:1 mixture of Alamar Blue reagent and 10 % tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth.

Anti-Inflammatory Activity

A solution of 0.2 % w/v of Bovine serum albumin (BSA) was prepared in Tris buffer saline and pH was adjusted to 6.8 using glacial acetic acid. Stock solutions of 1000 μ g /ml of all test samples were prepared by using methanol as a solvent. From the stock solutions two different concentrations of 100 μ g /ml and 200 μ g /ml were prepared by using methanol as a solvent. 100 μ g /ml of each test sample was taken to which 5ml of 0.2 % BSA was added. The control consists of 5ml 0.2 % w/v BSA solution with 0.1ml methanol. The 0.1ml standard contains 100 μ g /ml of Indomethacin in methanol with 5ml 0.2 % w/v BSA solution. The volumetric flasks were heated at 72°C for 5 minutes and then cooled for 10 minutes. The absorbance of these solutions was determined by using spectrophotometer at a wavelength of 660 nm. The % denaturation of the protein (% inhibition) was determined by using formula as given.

$$\% \text{ inhibition} = \frac{\text{Absorbance of Control} - \text{Absorbance of Test}}{\text{Absorbance of Control}} \times 100$$

CONCLUSION

In the conclusion novel acryloyl phenyl chromene-4-one derivatives were synthesized and proved by spectral data. All the synthesized compounds were screened for In-vitro anti-inflammatory activity by Bovine Serum Albumin method. Compounds CN - 2, 5, 7 were active at very low dose of 100 µg/ml and CN - 1, 2, 5, 6, 7, 8, 9 have showed dose dependant activity, exhibiting moderate activity of 50-60 % inhibition of inflammation. This activity would be attributed due to presence of trimethoxy, dimethoxy and hydroxyl group of the substituted chalcone.

The new acryloyl phenyl chromone-4-one derivatives have shown promising results against *M. Tuberculosis* ATTS 27294, indicating the flavones moiety may be contributing for activity. The efficacy of activity was not altered by cyclization of chalcone to pyrimidine nucleus for CN 3, CN 5 and CN 7, demonstrates chalcone moiety may be responsible for their positive results. Sensitivity towards *M. Tuberculosis* for compound CN 1 can purely be attributed to for the trimethoxy group of chalcone moiety along with flavone moiety.

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REFERENCES

- 1.Pandurangan N, Bose C, Banergi A. Synthesis and Antioxygenic activities of seabuckthorn flavones-3-ols and analogs. *Bioorg Med ChemLett*, 2011; 21:5328-5330.
- 2.Harborne BJ, Williams CA, Advances in flavonoids since 1192. *Nat Prod Rep*, 2001; 18:310-315.
- 3.Whitting DA. Chemistry of flavonoids. *Nat Prod Rep*, 2001; 18:583-591.
- 4.Rao YK, Rao CV, Kishore PH, Gunasekar D. Flavonol as a natural product. *J Nat Prod*, 2001; 64:368-373.
- 5.Helavi YB, Solabannavar SB, Salunkhe RS, Mane RB. Chemistry and synthesis of new flavone derivatives. *J Chem Res Synop*, 2003; 279-289.
- 6.Seijas JA, Vazues TMP, Carballido RR, Synthesis and antioxidant activity of some novel flavone derivatives. *J Org Chem*, 2005; 70:2855-2867.
- 7.Morimoto M, Tanimoto K, Nakano S, Ozaki T, Nakano A, Komai K. Chemistry, synthesis and biological evaluation of some novel flavonoid derivatives. *J Agric Food Chem*, 2003; 51:389-398.
- 8.K Elumalai, MA Ali, M Elumalai, K Eluri, S. Srinivasan, *J Acute Disease.*, 2011, 321.
- 9AR Trivedi, DK K. Dodiya, NR Ravat, VH Shah. *ARKIVOC.*, 2008, Xi, 141.
- 10.CMBhalgat, MI Ali, B Ramesh, G Ramu, Ara J *Chem.*, 2011, 8.