Heterocyclic Letters
Vol. 5 | No.4|601-608| Aug-Oct| 2015
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

MICROWAVE ASSISTED ENVIRONMENTALLY BENIGN APPROACH TO THE SYNTHESIS OF SOME NOVEL MANNICH'S BASES OF 3-(N-HETRYL AMINO METHYL ISTAIN)HYDRAZONES

Pramila Sharma, Navjeet Kaur and D. Kishore

Department of Chemistry, Banasthali University, Banasthali (RAJ. 304022)
E-mail: nvjithaans@gmail.com

Abstract:
Microwave assisted facile one pot synthesis of novel N-Hetryl amino methyl indoline-2,3-diones **(3-7)** were prepared from the reaction of isatin (indoline-2,3-dione) with formaldehyde and hetryl amines such as dimethyl amine, piperidine, morpholine, N-ethyl piperazine and pyrrolidine.

Keywords: Morpholine, piperidine, piperazine, pyrrolidine, isatin.

Introduction:

1,4-Bezodiazepines belong to the class of privileged structures. [1-2] Development of methodologies to facilitate the preparation of compound libraries based on the privileged structures is an intense area of research. Due to the vast commercial success and medicinal utility of the heterocyclic scaffolds such as pyridines, morpholines, piperazines, 2-amino (pyridines, pyrimidines, benzothiazoles) etc. in drug design and synthesis, various methods to incorporate these pharmacophores in 1,4-benzodiazepines (mostly on 2-position) has been developed. [3-4]

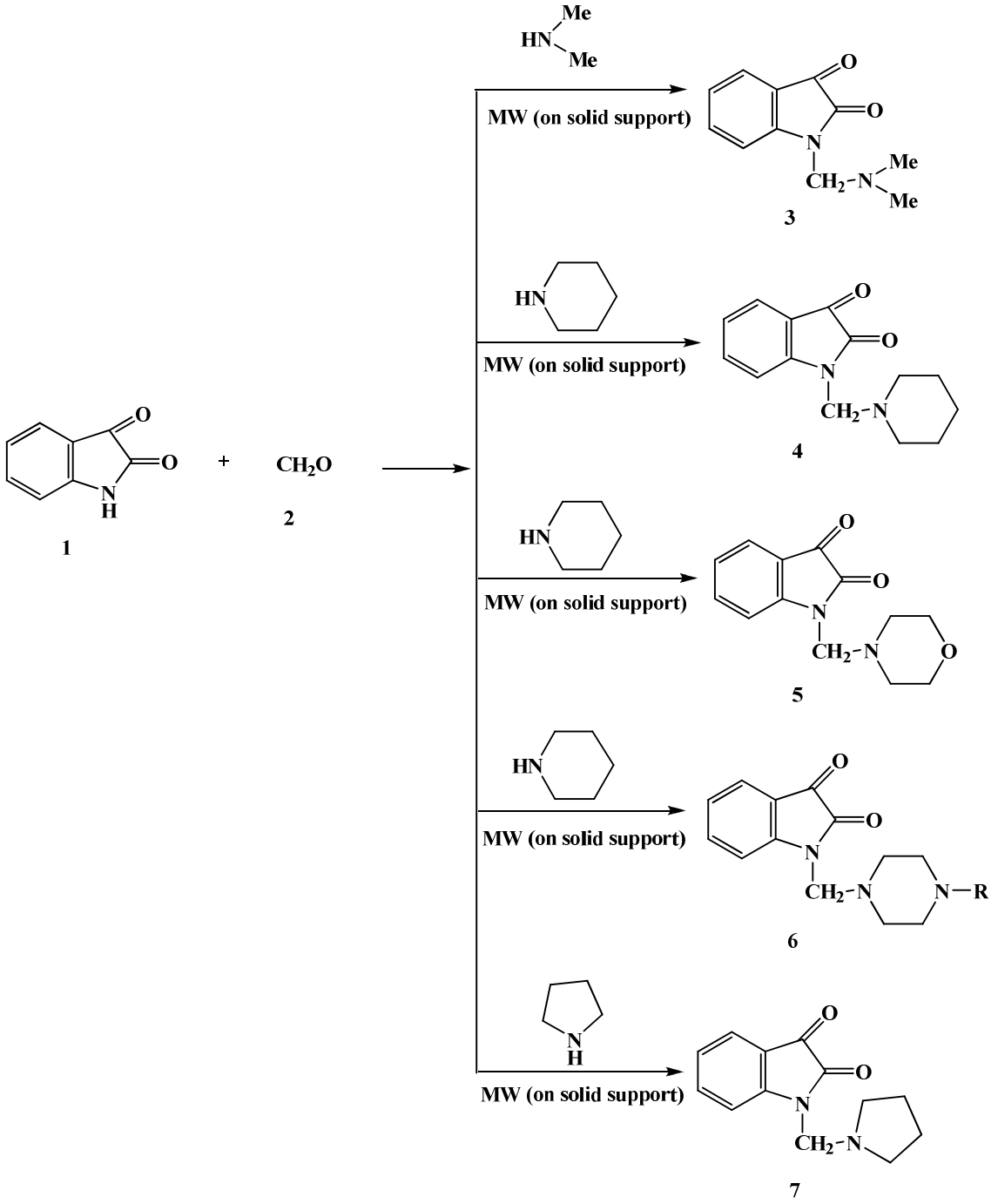
It was interesting to note that incorporation of isatin with a variety of substituted amino pyrimidinyl derivatives showed an incredible potency enhancing effect in both enzymes and antiviral assays [5-7]. A recent work, on these compounds has identified several novel aminopyrimidinimino isatin analogues exhibiting a broad spectrum of chemotherapeutic properties in combating HIV and OIS (the opportunistic infections like TB, viral, fungal, protozoal and neoplastic diseases etc.). From this study, the compound, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[3'-(4'-amino-5'-trimethoxybenzyl pyrimidine-2'-yl)imino-1-(5-fluoroisatinyl)]-N'-piperazinyl]-3-quinoline carboxylic acid in which one can easily discern the portion of isatin, (present as its N-Mannich's base), fragment of amino pyrimidines (containing a trimethoxy benzyl substituent) and quinoline carboxylic acid moiety (to which a piperazine fragment may be seen to be appended) emerged as the most potent broad-spectrum chemotherapeutic agent active against HIV, HCV, Mycobacterium tuberculosis and various other pathogenic bacteria [8-11].

Inspired by these interesting findings on the pharmacological properties of the molecules derived from isatins, the isatin molecule was appended with the Mannich's base fragments to generate the lead structures **(3-7)**. It has been observed that incorporation of certain bioactive pharmacophores in the existing drug molecules sometimes exerts a profound influence on the

biological profiles of that molecule [12]. It has been observed recently that incorporation of Mannich's base fragment in the existing drug enhances the biological activity of the molecules by providing an additive effect on the overall potency of the molecules. Our motivation towards the incorporation of the Mannich's base on isatin's was based on the premise that their presence in tandem in the same molecular framework should contribute significantly to the biological activity in the resulting molecules [13].

In view of the above precedence in the literature [14-15], it was considered worthwhile in the present work, to synthesize some such molecules in which a few selected bioactive pharmacophores were brought together in such a way so as to become the part of a single structure. The idea behind formulating such a study was to assess the favourable impact if any, they produced on the biological activity in the new molecules through the additive or cumulative effects exercised by each of these moieties. If their role to produce a positive impact on activity was established such structures were likely to form interesting targets in synthesis and in biological evaluations.

In view of the wide applicability of the microwave irradiation technique in chemical reaction rate enhancements, facilitating the reactions to take place in an environment friendly atmosphere, in a single pot, in less time, with higher yields, allowing the saving of time and energy both, we utilized this technique in the present work. Structure of all the compounds were established on the basis of their microanalyses, IR, ^{1}HNMR and MS spectral data.



Scheme-1

Experimental:

All melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on KBr disc using Perkin Elmer-1800 intrachord. ^{1}H NMR spectra were recorded in $CDCl_3$ on Brucker Avance 400 MHz spectrophotometer with TMS as internal standard (chemical shifts are expressed in δ ppm). The mass spectra were recorded on a Joel SX-102 (EI/CI/FAB) mass spectrometer at 70 eV. The reactions were monitored by the TLC on silica gel G plates in the solvent system benzene-methanol mixture (9:1).

Microwave activation coupled with dry media technique (using the solid supports) was applied in the synthesis of compounds **3-7**.

Preparation of 1((dimethylamino)methyl) indoline-2-3-dione (3).

Solution phase microwave assisted method:

Equimolar quantities of isatin (0.147 g, 0.001 mole), dimethylamine (0.045 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was taken in ethanol (10 ml) and placed in 100 ml flask fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation at 360 W microwave power, for 5 min and then at 720 W for 4 min with short interval of 1 min to avoid the excessive evaporation of solvent. The completion of the reaction was checked by TLC. The solution obtained after the reaction had completed was kept at 0 °C for 1 h. and the resulting solid obtained was filtered and recrystallized from ethanol to give **3**, 0.28 g. (yield 68.0%), m.p. 145-147 °C.

Solid phase microwave assisted method:

A slurry of equimolar quantities of isatin (0.147 g, 0.001 mole) dimethylamine (0.045 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was adsorbed over basic alumina (2.0 g) via a solution in ethanol (3 ml). The dried slurry was powdered and the free flowing powder was placed in a 100 ml borosil beaker and irradiated at (360 W) microwave power for 5 min and then at 720 W for 2 min until the completion of the reaction (monitored by TLC). The recyclable inorganic solid support was separated by extracting the product with ethyl acetate The solvent was evaporated and the solid obtained was recrystallized from dichloromethane and dried to give **3,** 0.21 g (yield 91.0 %), m.p.145-147 °C.

Preparation of (1((piperidin-1-yl)methyl)indolin-2-3-dione (4).

Solution phase microwave assisted method:

Equimolar quantities of isatin (0.147 g, 0.001 mole), piperidine (0.085 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was taken in ethanol (10 ml) and placed in 100 ml flask fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation at 360 W microwave power, for 5 min and then at 720 W for 4 min with short interval of 1 min to avoid the excessive evaporation of solvent. The completion of the reaction was checked by TLC. The solution obtained after the reaction had completed was kept at 0 °C for 1 h. and the resulting solid obtained was filtered and recrystallized from ethanol to give **4**, 0.15 gm (yield 71.4%), m.p. 155-158 °C.

Solid phase microwave assisted method:

A slurry of equimolar quantities of isatin (0.147 g, 0.001 mole) piperidine (0.085 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was adsorbed over basic alumina (2.0 g) via a solution in ethanol (3 ml). The dried slurry was powdered and the free flowing powder was placed in a 100 ml borosil beaker and irradiated at (360 W) microwave power for 5 min and then at 720 W for 2 min until the completion of the reaction (monitored by TLC). The recyclable inorganic solid support was separated by extracting the product with ethyl acetate The solvent was evaporated and the solid obtained was recrystallized from dichloromethane and dried to give **4**, 0.21g (yield 92%), m.p. 155-158 °C.

Preparation of 1-(morpholin-1yl-methyl) indoline-2-3-dione (5).

Solution phase microwave assisted method

Equimolar quantities of isatin (0.147 g, 0.001 mole), morpholine (0.87 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was taken in ethanol (10 ml) and placed in 100 ml flask fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation at 360 W microwave power, for 5 min and then at 720 W for 4 min with short interval of 1 min to avoid the excessive evaporation of solvent. The completion of the reaction was checked by TLC. The solution obtained after the reaction had completed was kept at 0 °C for 1 h and the resulting solid obtained was filtered and recrystallized from ethanol to give **5**, 0.16 gm (yield 72.3%), m.p. 188-190 °C.

Solid phase microwave assisted method:

A slurry of equimolar quantities of isatin (0.147 g, 0.001 mole), morpholine (0.87 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was adsorbed over basic alumina (2.0 g) via a solution in ethanol (3 ml). The dried slurry was powdered and the free flowing powder was placed in a 100 ml borosil beaker and irradiated at (360 W) microwave power for 5 min and then at 720 W for 2 min until the completion of the reaction (monitored by TLC). The recyclable inorganic solid support was separated by extracting the product with ethyl acetate The solvent was evaporated and the solid obtained was recrystallized from dichloromethane and dried to give **5**, 0.21 g (yield 93.2%), m.p. 188-190 °C.

Preparation of 1(4-ethylpiperazin-1-yl)methyl, indoline-2-3-dione (6).

Solution phase microwave assisted method:

Equimolar quantities of isatin (0.147 g, 0.001 mole), N-ethyl piperazine (0.87 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was taken in ethanol (10 ml) and placed in 100 ml flask fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation at 360 W microwave power, for 5 min and then at 720 W for 4 min with short interval of 1 min to avoid the excessive evaporation of solvent. The completion of the reaction was checked by TLC. The solution obtained after the reaction had completed was kept at 0 °C for 1 h and the resulting solid obtained was filtered and recrystallized from ethanol to give **6**, 0.16 gm (yield 68.5%), m.p. 190-192 °C.

Solid phase microwave assisted method:

A slurry of equimolar quantities of isatin (0.147 g, 0.001 mole) N-ethyl piperazine (0.87 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was adsorbed over basic alumina (2.0 g) via a solution in ethanol (3 ml). The dried slurry was powdered and the free flowing powder was placed in a 100 ml borosil beaker and irradiated at (360 W) microwave power for 5 min and then at 720 W for 2 min until the completion of the reaction (monitored by TLC). The recyclable inorganic solid support was separated by extracting the product with ethyl acetate The solvent was evaporated and the solid obtained was recrystallized from dichloromethane and dried to give **6**, 0.22 g (yield 90.5%), m.p. 190-192 °C.

Preparation of 1-((pyrrolidin-1-yl)methyl), indoline-2-3-dione (7).

Solution phase microwave assisted method:

Equimolar quantities of isatin 0.147 g, 0.001 mole), pyrrolidin (0.87 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was taken in ethanol (10 ml) and placed in 100 ml flask fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation at 360 W microwave power, for 5 min and then at 720 W for 4 min with short interval of 1 min to avoid the excessive evaporation of solvent. The completion of the reaction was checked by TLC. The solution obtained after the reaction had completed was kept at 0 °C for 1 h and the resulting solid obtained was filtered and recrystallized from ethanol to give **7**, 0.16 g (yield 68.5%), m.p. 190-192 °C.

Solid phase microwave assisted method:

A slurry of equimolar quantities of isatin (0.147 g, 0.001 mole), pyrrolidin (0.87 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was adsorbed over basic alumina (2.0 g) via a solution in ethanol (3 ml). The dried slurry was powdered and the free flowing powder was placed in a 100 ml borosil beaker and irradiated at (360 W) microwave power for 5 min and then at 720 W for 2 min until the completion of the reaction (monitored by TLC). The recyclable inorganic solid support was separated by extracting the product with ethyl acetate The solvent was evaporated and the solid obtained was recrystallized from dichloromethane and dried to give **7**, 0.22 g (yield 90.5%), m.p. 190-192 °C.

Results and Discussion:

Mannich's bases tend to enhance the biological activities of the molecule and proved to be of immense significance in providing an additive effect on the biological profiles of the molecules. Isatin nucleus is very prone to give Mannich's reaction with formaldehyde and secondary amines and this reaction has been shown recently [16] to occur on isatin with great facility under microwave conditions using solvent or alternatively using the basic alumina as the inorganic solid support in the reaction. Isatin nitrogen in **1** reacted smoothly in the present work with formaldehyde and secondary amines viz; pyrrolidine, piperidine, morpholine, 1-ethyl piperazine under microwave conditions to give **3-7 (Scheme 1)**.

In view of the impressive biological activities shown by isatin and heterocyclic amines, it was thought of interest in the present work to construct a system, which carried isatin and fragments derived from heterocyclic amines in the same molecular framework. The idea behind building such a system was to incorporate the biological activities of the three well established molecules, the isatin and heterocyclic primary and secondary amines in a single molecular frame work. It was envisaged that a molecule which could allow these systems to hold together and was accessible easily, was isatin. The synthesis of the proposed molecules **(3-7)** was conceived in the present work under microwave conditions from isatin following the strategy shown in **Scheme 1**. Isatin has been known to react readily with formaldehyde and sec. amines to give the Mannich's bases. In the present work isatin was treated with formaldehyde and sec. amines such as pyrrolidine morpholine piperidine and N-substituted piperazines to give the Mannich's bases. This strategy was applied on isatin under microwave conditions to give **3-7**. In an alternate procedure MW reaction was done in dry media using basic alumina as a solid support to give a nearly quantitative yield of **3-7** from isatin.

Acknowledgement:

Authors are thankful to Punjab University, Chandigarh for providing the spectral data of the compounds. Authors are highly thankful for financial support provided by Department of Science and Technology (DST), New Delhi to "Banasthali Center for Education and Research in Basic Sciences" under their CURIE (Consolidation of University Research for Innovation and Excellence in women Universities) programme.

References:

[1] (a) Evans, B.E.; Rittle, K.E.; Bock, M.G.; Dipardo, R.M.; Freidinger, R.M.; Whitter, W.L.; Lundell, G.F.; Veber, D.F.; Anderson, P.S.; *J. Med. Chem.* **1988,** 31, 2235. (b) Kaur, N. *J. Iranian Chem. Soc.* **2015**, 12, 9. (c) Kaur, N.; Kishore, D. *J. Heterocycl. Chem.* **2014**, 51, E340. (d) Kaur, N.; Kishore, D. *J. Chem. Sci.* **2014**, 126, 1861. (e) Kaur, N.; Kishore, D. *Synth. Commun.* **2014**, 44, 2789.

[2] (a) Patchett, A.A.; Nargund, R.P.; *Annu. Rep. Med. Chem.* **2000,** 35, 289. (b) Kaur, N.; Kishore, D. *J. Chem. Sci.* **2013**, 125, 555. (c) Kaur, N.; Tyagi, R.; Srivastava, M.; Kishore, D. *J. Heterocycl. Chem.* **2014**, 51, E50. (d) Kaur, N.; Kishore, D. *Synth. Commun.* **2014**, 44, 1375. (e) Kaur, N.; Kishore, D. *Synth. Commun.* **2014**, 44, 2577.

[3] (a) Laura, C.; Ana, A.C.; Cristina, A.; Davide, B. *Curr. Med. Chem.* **2009,** 9, 1. (b) Kaur, N. *Int. J. Pharma. Bio. Sci.* **2013**, 4, 366. (c) Kaur, N. *Int. J. Pharma. Bio. Sci.,* **2013**, 4, 318. (d) Kaur, N. *Int. J. Pharma. Bio. Sci.* **2013**, 4, 357.

[4] (a) Giuseppe, C.; Alba, C.; Silvana, C.; *Heterocycles*, **1985,** 23, 2051. (b) Kaur, N. *Int. J. Pharma. Bio. Sci.* **2013**, 4, 485. (c) Sharma, P.; Kaur, N.; Sirohi, R.; Kishore, D. *Bull. Chem. Soc. Ethiopia,* **2013**, 27, 301. (d) Kaur, N.; Sharma, P.; Sirohi, R.; Kishore, D. *Archiv. Appl. Sci. Res.* **2012**, 4, 2256.

[5] Moore, M. B.; Rapola, R. T. *J. Am. Chem. Soc*. **1946**, 68, 1657.

[6] Kabalka, G. W.; Pagni, R. M. *Tetrahedron,* **1997**, 53, 7999.

[7] Sayed, E. I. H.; Tamany, E. I. M.; Din, E. I. E.; Salim, M. *J. Indian Chem. Soc.* **1997,** 74,772.

[8] Varma, R. S. *J. Pharm. Sci.* **1973**, 62, 1390.

[9] Varma, R. S.; Garg, P. K.; Verma, H. N.; Awasthi, L. P. *Arch. Pharm*. **1981**, 314, 918.

[10] De Wolfe, W. G. *Young, Chem. Rev*. **1956,** 56, 753.

[11] Rao, G. V. P.; Reddy, P. N.; Reddy, Y. T.; Kumar, V. N.; Rajitha, B. *Ind. J. Chem*. **2005**, 44B, 1109.

[12] Lehmann, F.; Pilotti, A.; Luthman, K. *Indian J. Chem.* **2003**, 7, 145.

[13] Mahesh, R.; Perumal, R. V. *Indian J. Chem*. **2004**, 43B, 1012.

[14] Mogilaiah, K.; Sakram, B. *Indian J. Chem*. **2004**, 43B, 2724.

[15] Kataki, D.; Phukan, P. *Indian J. Chem*. **2006**, 45B, 1759.

[16] Ghantwal, S. R.; Samant, S. D. *Indian J. Chem.* **1999**, 77, 100.

Table 1: Physical and Analytical data of the compounds 3-7:

S. No.	Compd	Molecular Formula	M.W.	M.P.(˚C)	Yield (%)		Elemental analysis	
					MW Solvent phase	MW Solid phase	(cald./ found) N	(cald./ found) S
1.	3	$C_{11}H_{12}N_2O_2$	204.23	145-47	71.12	91.4	13.72/20.30	-
2.	4	$C_{11}H_{14}N_2O_3$	246.26	155-58	71.4	92.3	11.38/17.24	-
3.	5	$C_{14}H_{16}N_2O_2$	244.12	188-90	72.3	93.2	11.47/16.83	-
4.	6	$C_{13}H_{19}N_3O_2$	273.33	190-92	68.5	90.5	15.37/9.04	-
5.	7	$C_{13}H_{14}N_2O_2$	230.26	170-72	68.0	91.0	12.17/17.08	-

Table 2: Spectral data of compounds 3-7:

S. No.	Compound	IR (KBr) cm^{-1}	^1H NMR ($CDCL_3$+DMSO-d_6) δ(ppm)
1.	3	2990, 1730, 1680, 1589	7.83-7.52 (m, 4H, ArH), 4.03 (s, 2H, CH_2), 2.27 (s, 6H, CH_3),
2.	4	2930, 1720, 1660, 1590	7.88-7.42 (m, 4H, ArH), 4.03 (s, 2H, CH_2), 3.34 (t, 4H, $(CH_2)_2$), 1.50 (m, 6H, $(CH_2)_3$)
3.	5	2980, 1730, 1640, 1595	7.65-7.48 (m, 4H, ArH), 4.15 (s, 2H, CH_2), 3.67 (t, 4H, $(CH_2)_2$),

			2.37 (t, 4H, $(CH_2)_2$)
4.	6	2980, 1725, 1645, 1595	7.90-7.62 (m, 4H, ArH), 4.05 (s, 2H, CH_2), 2.46 (m, 8H, CH_2), 2.40 (q, 2H, CH_2), 1.00 (t, 3H, CH_3)
5.	7	2940, 1720, 1670, 1585	7.93-7.65 (m, 4H, ArH), 4.10 (s, 2H, CH_2), 2.25 (t, 4H, CH_2), 1.59 (m, 4H, CH_2)

Received on August 27, 2015.