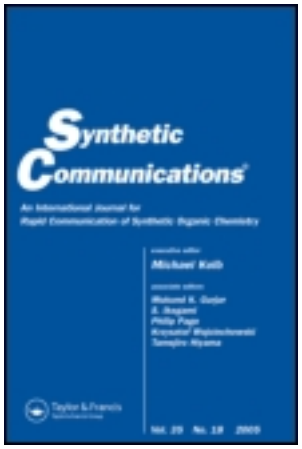


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Approach to Pure Entacapone and Related Compounds

G. Srikanth [a b], Uttam Kumar Ray [a], D. V. N. Srinivas Rao [a], P. Badarinadh Gupta [a], P. Lavanya [a] & Aminul Islam [a]

[a] Chemical Research and Development, Aurobindo Pharma Limited, Hyderabad, India

[b] Jawaharlal Nehru Technological University, Hyderabad, India

Accepted author version posted online: 21 Oct 2011. Version of record first published: 11 Jan 2012

To cite this article: G. Srikanth, Uttam Kumar Ray, D. V. N. Srinivas Rao, P. Badarinadh Gupta, P. Lavanya & Aminul Islam (2012): Efficient Approach to Pure Entacapone and Related Compounds, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:9, 1359-1366

To link to this article: http://dx.doi.org/10.1080/00397911.2010.539894

Synthetic Communications®, 42: 1359–1366, 2012

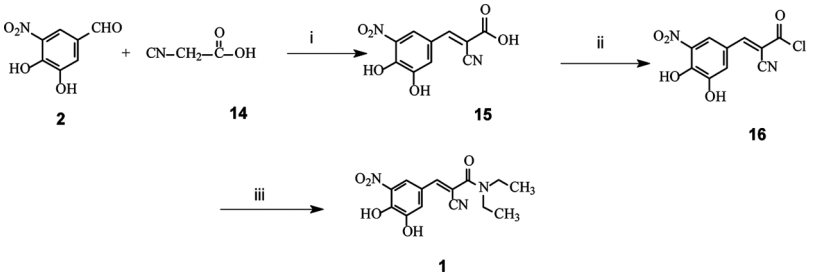
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.539894

EFFICIENT APPROACH TO PURE ENTACAPONE AND RELATED COMPOUNDS

G. Srikanth,[1,2] Uttam Kumar Ray,[1] D. V. N. Srinivas Rao,[1] P. Badarinadh Gupta,[1] P. Lavanya,[1] and Aminul Islam[1]

[1]*Chemical Research and Development, Aurobindo Pharma Limited, Hyderabad, India*
[2]*Jawaharlal Nehru Technological University, Hyderabad, India*

GRAPHICAL ABSTRACT



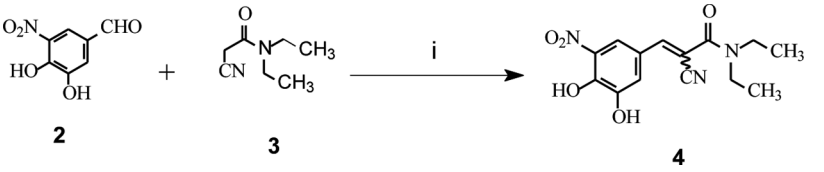
Abstract *A new and efficient process through a new intermediate, (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nirtrophenyl)prop-2-enoic acid* ***15****, has been described for preparing substantially pure entacapone* ***1****. This new intermediate* ***15*** *was prepared by Knoevenagel condensation of 3,4-dihydroxy-5-nitrobenzaldehyde* ***2*** *with 2-cyanoacetic acid* ***14*** *and was further condensed with diethylamine to get pure entacapone* ***1****. Some of the important process-related impurities of entacapone (****17****,* ***18****,* ***19****, and* ***20****) were also prepared easily from this intermediate* ***15****.*

Keywords Aluminum chloride; cyanoacetic acid; impurities; Knoevenagel condensation; Parkinson's disease; piperidine

INTRODUCTION

Entacapone **1,** chemically known as (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N,N*-diethylprop-2-enamide, is a catechol-O-methyl transferase (COMT) inhibitor.[1,2] Entacapone **1** is approved under the trademark Comtan by the U.S. Food and Drug Administration for the treatment of Parkinson's disease.[3,4] Many synthetic approaches have been reported for the synthesis of entacapone **1**.[5–10] The

Received September 10, 2010.
Address correspondence to Uttam Kumar Ray, Chemical Research and Development, Aurobindo Pharma Limited, Hyderabad 500 072, Andhra Pradesh, India. E-mail: ukray@aurobindo.com



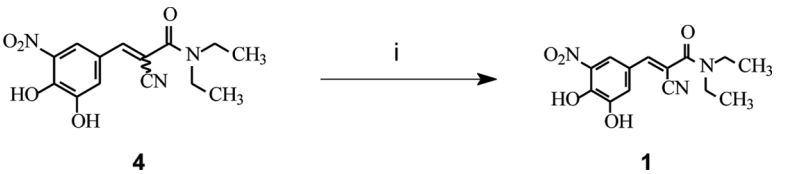
Scheme 1. (i) Piperidineacetate, ethanol, reflux.

first process for the synthesis of entacapone **1** was disclosed by Backstrom et al.[5,6] They prepared entacapone **1** along with a mixture of two geometric isomers **4**, wherein the ratio of *E*/*Z* isomers is approximately 70:30 through the condensation reaction between 3,4-dihydroxy-5-nitrobenzaldehyde **2** and *N,N*-diethyl-2-cyanoacetamide **3** (Scheme 1). However, they have not reported any crystallization methods to remove the unwanted *Z*-isomer from the mixture.

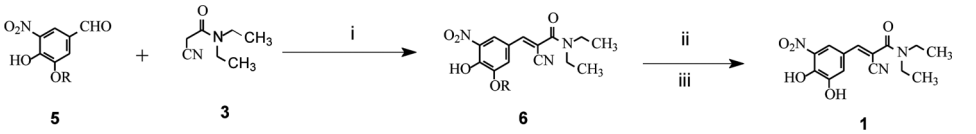
Further, Pippuri et al.[7] also prepared entacapone **1** by following this method, they but crystallized the mixture of isomers **4** from lower aliphatic carboxylic acid, such as a HCOOH and CH_3COOH in the presence of catalytic amounts of HCl or HBr to obtain pure entacapone **1** (Scheme 2).

Venkateshwarulu et al.,[8] disclosed the preparation of **1** from 3-O-alkylated entacapone **6,** which in turn is prepared by condensing 3-alkoxy-4-hydroxy-5-nitrobenzaldehyde **5** with *N,N*-diethyl-2-cyanoacetamide **3**. 3-O-Alkylated entacapone **6** on treatment with $AlCl_3$ results in the mixture of **4**, which is purified by crystallization using a mixture of methanol and toluene to get pure entacapone **1** (Scheme 3).

All these processes have some drawbacks such as longer reaction time, use of hazardous and corrosive reagents, and need for crystallization by purification to remove unwanted isomer to get the pure entacapone **1**. In another report by Cziaky et al.,[9] vanillin **7** is reacted with *N,N*-diethyl-2-cyanoacetamide **3**. The

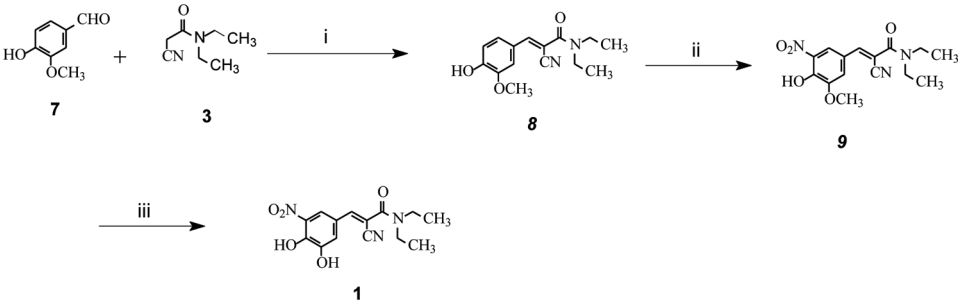


Scheme 2. (i) CH_3COOH, HBr, 90 °C.



R = methyl or ethyl

Scheme 3. (i) Piperidine, CH_3COOH, toluene, 110 °C; (ii) $AlCl_3$, 5 °C; and (iii) methanol and toluene.

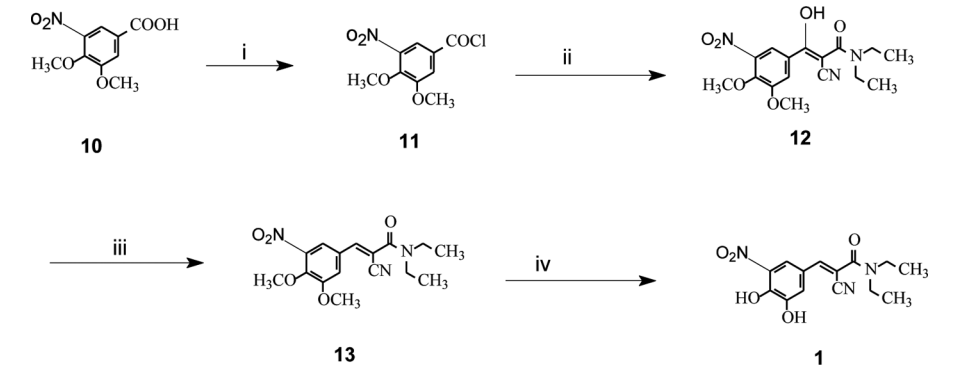


Scheme 4. (i) Diethyl amine, CH_3COOH, toluene, reflux; (ii) HNO_3; and (iii) $AlCl_3$, DMF, 100 °C.

resulting (2*E*)-2-cyano-3-(3-methoxy-4-hydroxy-phenyl)-*N,N*-diethylprop-2-enamide **8** is nitrated to get (2*E*)-2-cyano-3-(3-methoxy-4-hydroxy-5-nitro-phenyl)-*N,N*-diethylprop-2-enamide **9**, which is demethylated to give crude entacapone (Scheme 4). This crude product is purified from isopropyl alcohol and then from a mixture of acetone and acetic acid to give entacapone **1**. The main drawbacks of the method are longer reaction time, use of hazardous and corrosive reagents, and requirement for recrystallization to obtain pure entacapone **1**.

Sanmarti et al.,[10] reported another method for synthesis of entacapone **1**, which is depicted as shown (Scheme 5). In this route, 3,4-dimethoxy-5-nitrobenzoic acid **10** was treated with $SOCl_2$ to get 3,4-dimethoxy-5-nitrobenzoylchloride **11**, which is then reacted with *N,N*-diethyl-2-cyanoacetamide **3** to get 2-cyano-3-(3,4-dimethoxy-5-nitrophenyl)-3-hydroxy-*N,N*-diethyl-prop-2-enamide **12**. Reaction of **12** with $NaHB(OAc)_3$ results in 3,4-dimethoxy entacapone **13**, which is then demethylated to give entacapone **1** (Scheme 5).

In this process also, hazardous chemicals such as $AlCl_3$ and NaH have been used. It is obvious that there is a need to have a better process for the preparation of entacapone **1**. We report here an efficient synthesis of entacapone **1**.



Scheme 5. (i) $SOCl_2$, toluene, 60 °C; (ii) NaH, *N,N*-diethyl-2-cyanoacetamide, THF, −5 °C; (iii) $NaHB(OAc)_3$, 45 °C; and (iv) $AlCl_3$, pyridine, 80 °C.

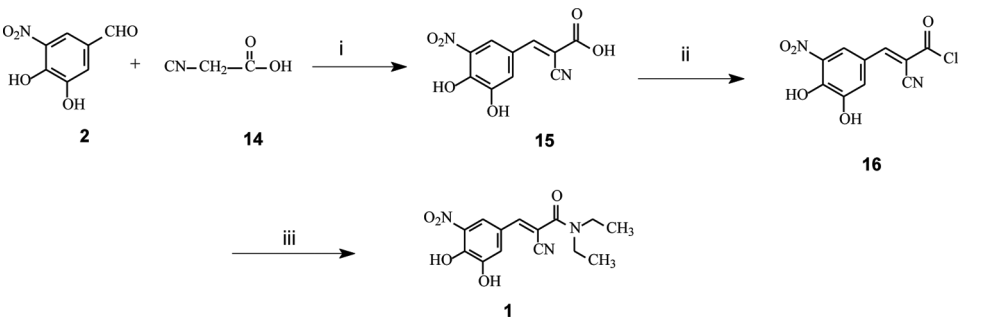
RESULTS AND DISCUSSION

The condensation reaction of the 3,4-dihydroxy-5-nitrobenzaldehyde **2** with *N,N*-diethyl-2-cyanoacetamide **3** proceeds as per the Knoevenagel condensation. This Knoevenagel condensation reaction is very useful and widely used in synthetic organic chemistry.[11–16] However, it is also reported in many cases that condensation will not produce always the pure *cis* (*Z*) or *trans* (*E*) isomeric compounds.[11–16] The selectively formation of the isomers depend on the condition of reaction and the nature of the substitutent in the active methylene compounds.[13,15] Inokuchi et al.[13] have worked on the Knoevenagel condensation on different aromatic aldehyde and active methylene compounds and reported the formation of mixture of *E* and *Z* isomers. Similarly, as described in the first process of Backstrom et al.,[5,6] condensation between 3,4-dihyrroxy-5-nitrobenzaldehyde **2** and *N,N*-diethyl-2-cyanoacetamide **3** results in the mixture of *E* and *Z* isomers of entacapone **4** in the ratio of 70:30. This is the major drawback of this process, and further crystallization is required to remove the undesired *Z*-isomer, thereby resulting in poor yield.

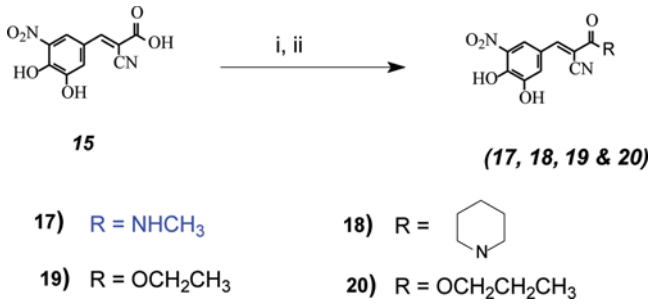
To circumvent these difficulties, we have devised an efficient process for the preparation of substantially pure entacapone **1** through a new intermediate (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nirtrophenyl) prop-2-enoic acid **15**, which is prepared by Knoevenagel condensation between the 3,4-dihydroxy-5-nitrobenzaldehyde **2** and 2-cyanoaceticacid **14**. Compound **15** is obtained with good yield and purity. The major advantages of this new intermediate preparation are shorter reaction time and no need for further purification to get pure *E*-isomer of compound **15**.

Compound **15** was converted into its corresponding chloride **16** using thionyl chloride. This chloride **16** was condensed with diethyl amine to yield entacapone **1** (Scheme 6), which is highly pure. The formation of intermediate **15** is stereoselective and yields mostly pure (*E*)-isomer. With this quantity of intermediate **15**, we are able to prepare pure Entacapone **1** having $<0.1\%$ undesired *Z*-isomer. The content of *E* and *Z* isomers in entacapone is determined through high-pressure liquid chromatography (HPLC).[17]

Using this efficient method for the preparation of entacapone **1**, we have successfully prepared some of the related compounds of entacapone **1**, which may be present as impurities in entacapone. The related compounds **17**, **18**, **19**, and **20** have been reported[17] as impurities in entacapone. These impurities are prepared as per



Scheme 6. (i) Piperidine, CH_3COOH, ethanol, 80 °C; (ii) $SOCl_2$, 80 °C; and (iii) diethyl amine, 0 °C.



Scheme 7. (i) $SOCl_2$, 80 °C; and (ii) R-H, 0 °C. (Figure is provided in color online.)

the process depicted in Scheme 7 with good yield and purity. All these compounds (**17**, **18**, **19**, and **20**) are well characterized by ^{1}H NMR, ^{13}C NMR, Mass, and infrared (IR) analysis.

CONCLUSION

In conclusion, we have developed an efficient synthetic route for entacapone and some of its process-related impurities. Entacapone with substantiate purity will be prepared by this process without doing any extensive purification.

EXPERIMENTAL

Solvents and reagents were obtained from commercial sources and used without purification. Melting points were determined on a Polmon-melting point apparatus. All melting points were uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300-MHz spectrometer. The chemical shifts are reported in parts per million (δ ppm) relative to tetramethylsilane (TMS). The IR spectra were recorded in solid state as KBr dispersion using a Perkin-Elmer Fourier transform (FT)-IR spectrometer. The mass spectra were recorded on an API 2000 Perkin-Elmer PE-SCIEX mass spectrometer.

(2*E*)-2-Cyano-3-(3,4-dihydroxy-5-nirtrophenyl)prop-2-enoic Acid (15)

A mixture of 3,4-dihydroxy-5-nitrobenzaldehyde **2** (100 g, 547 mmol), 2-cyanoacetic acid **14** (69.67 g, 820 mmol), piperidine (86.1 g, 101 mmol), acetic acid (42 g, 700 mmol), and ethanol (900 ml) were heated to reflux for 4 h. The reaction mixture was concentrated under reduced pressure and then diluted with ethyl acetate (100 ml) and water (100 ml). The resulting solution was basified with 10% w/v aqueous sodium hydroxide solution (~200 ml). The aqueous layer was separated and acidified with concentrated HCl (~50 ml). The precipitate obtained was stirred for 1 h at 5 °C, filtered, and dried to get (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nirtrophenyl)prop-2-enoic acid **15** (80 g, 58.6%). Mp 124–126 °C; IR (KBr, cm^{-1}): 3255 (OH), 1684 (CO), 1364 (NO_2); ^{1}H NMR (DMSO-d_6, δ ppm): 7.87 (s, 1H, H-Ar), 8.O8 (s, 1H, H-Ar), 8.23 (s, 1H, H-C=C); ^{13}C-NMR (75 MHz, DMSO-d_6)

δ: 93.18, 109.3, 113.3, 118.1, 127.3, 135.1, 151.8, 153.7, 160.8, and 165.2; MS (ESI) m/z: 249 (M-H). Anal. calcd. for $C_{10}H_6N_2O_6$: C, 48.04; H, 2.42; N, 15.97. Found: C, 48.2; H, 2.45; N, 11.30.

(2*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N,N*-diethylprop-2-enamide (Entacapone 1)

(2*E*)-2-cyano-3-(3,4-dihydroxy-5-nirtrophenyl)prop-2-enoic acid **15** (5 g, 20 mmol) was added to $SOCl_2$ (25 ml) at 25–30 °C and heated for 4 h at 75 to 80 °C. The reaction mass was concentrated under reduced pressure to get residue (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nirtrophenyl)-2-propenoyl chloride **16**. The crude **16** in dichloromethane (50 ml) was added to a solution of diethyl amine (2.92 g, 40 mmol) in dichloromethane (50 ml) at −5 to 0 °C in 20 min and stirred for 2 h at −5 to 0 °C. Thereafter, the reaction mass was concentrated and diluted with ethyl acetate (50 ml) and water (50 ml). The solution was stirred for 30 min at 5 to 10°C. The organic layer was separated and concentrated under reduced pressure. Ethyl acetate (15 ml) was added to the residue. The slurry was stirred for 1 h at 5 to 10°C. The product was filtered and dried to get (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N,N*-diethylprop-2-enamide **1** (4 g, 65.5%). MP: 162–163°C; IR (KBr, cm^{-1}): 3339 (OH), 1628 (CO), 1372 (NO_2); ^{1}H NMR (DMSO-d_6, δ ppm): 1.15, (m, 6H, diethyl amine CH_3), 3.42 (m, 4H, diethyl amine CH_2), 7.64 (s, 1H, H-Ar), 7.76 (s, 1H, H-Ar), 7.93 (s, 1H, H-C=C), 10.95 (brs, 2H, OH); ^{13}CNMR (75 MHz, DMSO-d_6) δ: 12.8, 13.3, 40.3, 43.0, 104.8, 116.2, 117.8, 118.5, 122.8, 137.2, 144.9, 147.2, 148.0, and 162.7; MS (ESI) m/z: 304 (M-H). Anal. calcd. for $C_{14}H_{15}N_3O_5$: C, 55.13; H, 4.95; N, 13.77. Found: C, 55.2; H, 4.98; N, 13.9.

General Procedure for the Preparation of Impurities 17, 18, 19, and 20

(2*E*)-2-Cyano-3-(3,4-dihydroxy-5-nirtrophenyl)prop-2-enoic acid **15** (20 mmol) was added to $SOCl_2$ (25 ml) at 25–30 °C and heated for 4 h at 75 to 80 °C. Thionylchloride was removed under reduced pressure to get chloride **16**. This chloride **16** was reacted with monomethylamine (40 mmol) to precipitate compound **17** in dichloromethane (50 ml), reacted with piperidine (40 mmol) to precipitate compound **18** in dichloromethane (50 ml), reacted with ethanol (50 ml) to precipitate compound **19**, and reacted with n-propanol (50 ml) to precipitate compound **20**. Later on, precipitated compounds (**17**, **18**, **19**, and **20**) we isolated through filtration and further dried to obtain compounds **17**, **18**, **19**, and **20**. The spectral data for these compounds are presented.

(2*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*-methyl prop-2-enamide (17)

Mp: 246–250 °C. IR (KBr, cm^{-1}) 3429 (OH), 1623 (CO), 1352 (NO_2). ^{1}H NMR (DMSO-d_6, δ ppm) 2.73–2.74 (d, 3H, $J = 1.67$, methylamine CH_3), 7.79 (s, 1H, H-Ar), 7.96 (s, 1H, H-Ar), 8.05 (s, 1H, H-C=C), 8.33 (m, 1H, H-N-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 26.8, 104.3, 116.3, 118.2, 119.2, 122.2, 137.3, 145.4,

148.1, 148.7, 161.4; MS (ESI) m/z: 261.8 (M-H). Anal. calcd. for $C_{11}H_9N_3O_5$: C, 50.23; H, 3.44; N, 15.97. Found: C, 50.3; H, 3.50; N, 16.00.

(2*E*)-3-(3,4-Dihydroxy-5-nitrophenyl)-2-(piperidin-yl-1-carbonyl) prop-2-ennitrile (18)

Mp: 206–208 °C. IR (KBr, cm^{-1}) 3436 (OH), 1621 (CO), 1352 (NO_2). ^1H NMR (DMSO-d_6, δ ppm) 1.55–1.62 (m, 6H, piperidine CH_2), 3.52 (m, 4H, piperidine CH_2), 7.63 (s, 1H, H-Ar), 7.76 (s, 1H, H-Ar), 7.93 (m, 1H, H-C=C); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.6, 22.2, 23.8, 25.4, 43.8, 103.6, 116.4, 116.8, 119.1, 121.8, 136.9, 146.3, 147.8, 148.3, and 162.1; MS (ESI) m/z: 316 (M-H). Anal. calcd. for $C_{15}H_{15}N_3O_5$: C, 56.83; H, 4.76; N, 13.25. Found: C, 56.9; H, 4.78; N, 13.28.

Ethyl (2*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)prop-2-enoate (19)

Mp: 205–207 °C (lit.[5]). IR (KBr, cm^{-1}) 3230 (OH), 1620 (CO), 1356 (NO_2). ^1H NMR (DMSO-d_6, δ ppm) 1.28–1.33 (t, 3H, CH_3), 4.27–4.34 (q, 2H, OCH_2), 7.90 (s, 1H, H-Ar), 8.11 (s, 1H, H-Ar), 8.29 (s, 1H, H-C=C); ^{13}CNMR (75 MHz, DMSO-d_6) δ: 14.01, 62.23, 100.20, 115.69, 117.95, 121.12, 121.49, 137.34, 146.65, 148.20, 153.28, and 162.03; MS (ESI) m/z 277 (M-H). Anal. calcd. for $C_{12}H_{10}N_2O_6$: C, 51.84; H, 3.62; N, 10.07. Found: C, 51.86; H, 3.65; N, 10.10.

Propyl (2*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)prop-2-enoate (20)

Mp: 190–192 °C. IR (KBr, cm^{-1}) 3221 (OH), 1626 (CO), 1358 (NO_2). ^1H NMR (DMSO-d_6, δ ppm) 0.93–0.95 (t, 3H, CH_3), 1.64-1.68 (m, 2H, CH_2), 4.18–4.24 (t, 2H, OCH_2), 7.90 (s, 1H, H-Ar), 8.11 (s, 1H, H-Ar), 8.29 (s, 1H, H-C=C); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 10.18, 21.43, 67.55, 100.15, 115.61, 117.94, 121.2, 121.5, 137.26, 146.7, 148.24, 153.28, and 162.11; MS (ESI) m/z: 291 (M-H). Anal. calcd. for $C_{13}H_{12}N_2O_6$: C, 53.47; H, 4.14; N, 9.59. Found: C, 53.5; H, 4.20; N, 9.60.

ACKNOWLEDGMENTS

The authors thank the management of Aurobindo Pharma Ltd., Research and Development Centre, for supporting this work. The authors also thank the Analytical Research Department for their valuable contribution.

REFERENCES

1. Axelrod, J.; Tomchich, R. Enzymatic o-methylation of epinephrine and others catechols. *J. Biol. Chem.* **1958**, *233*, 702–705.
2. Cedarbaum, J. M. Clinical pharmacokinetics of anti-Parkinsonian drugs. *Clin. Pharmacokinetics* **1987**, *13*, 141–178.
3. Mannisto, P. T.; Kaakkolo, S. New selective COMT inhibitors: Useful adjuncts for Parkinson's disease? *Trends Pharamacol. Sci.* **1989**, *10*, 54–56.

4. Mannisto, P. T.; Kaakkolo, S. Rationale for selective COMT inhibitors as adjuncts in the drug treatment of Parkinson's disease. *Pharmacol. Toxicol.* **1990**, *66*, 317–323.
5. Backstrom, R.; Honkanen, E.; Pippuri, A.; Mannisto, P. T.; Kaakkola, S.; Pohto, P. Synthesis of some novel potent and selective catechol O-methyl transferase inhibitors. *J. Med. Chem.* **1989**, *32*, 841–846.
6. Backstom, R. J.; Heinola, K. E.; Honkanen, K. J.; Kaakkola, S. K.; Kairisalo, P. J.; Linden, Y.; Mannisto, P. I.; Nissinen, E. A. O.; Photo, P. Preparation of pyrocatechol derivatives for treating Parkinson's disease. Ger. Offen. DE Patent 3, 740,383, 1988; *Chem. Abstr.* **1988**, *109*, 128570x.
7. Pippuri, A.; Honkanen, E.; Haarala, T. Stable polymorphic form of *E-N,N*-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acryl amide and the process for its preparation. EP Patent 426468 1992; *Chem. Abstr.* **1991**, *115*, 214830n.
8. Venkateswarlu, J.; Veera Reddy, A.; Rajendiran, C.; Samjuddin, M. Methods for the preparation of entacapone. WO Patent 63,693, 2005; *Chem. Abstr.* **2005**, *143*, 115355 h.
9. Cziaky, Z. Process for the preparation of (*E*)-*N,N*-diethyl-2-cyano-3(3,4-dihydroxy-5-nitro-phenyl)-acryl amide in stable polymorphic form and intermediates of the process. WO Patent 2006064296, 2006; *Chem. Abstr.* **2006**, *145*, 83129k.
10. Sanmarti, B.; Rocabert, S.; Nicolau, P.; Ponce, M. Process for the preparation of entacapone and intermediates thereof. WO Patent 2008119793, 2008; *Chem. Abstr.* **2008**, *149*, 425635 t.
11. Balalaie, S.; Barajanian, M. Efficient and green procedure for the Knoevenagel condensation catalyzed by diammonium hydrogen phosphate in water. *Synth. commun.* **2006**, *36*, 2549–2557.
12. Kim, S. Y.; Kwon, P. S.; Kwon, T. N. Microwave-enhanced knoevenagel condensation of ethyl cyano acetate with aldehyde. *Synth. commun.* **1997**, *27*(4), 533–541.
13. Inokuchi, T.; Kawafuchi, H. E- or Z-selective Knoevengel condensation of acetoacetic derivatives: Effect of acylated substituent, that is, TEMPO and amines, as an auxiliary and new accesses to trisubstituted E- and Z-2-alkenals and furans. *J. Org. Chem.* **2006**, *71*, 947–953.
14. Augustine, J. K.; Naik, Y. K.; Mandal, A. B.; Chodappa, N.; Praveen, V. B. gem-Dibromomethylarens: A convenient substitute for noncommercial aldehyde in the Knoevenagel–Doebner reaction for the synthesis of the α,β-unsaturated carboxylic acids. *J. Org. Chem.* **2007**, *72*, 9854–9856.
15. Courtheyn, D.; Verhe, R.; Kimpe, M. P.; Buyck, L. D.; Schamp, N. Synthesis of electrophilic allyl dichlorides. *J. Org. Chem.* **1981**, *46*, 3226–3229.
16. Mukhopadhyay, C.; Datta, A. A simple, efficient, and green procedure for the knoevenagel condensation of aldehydes with *N*-methyl piperazine at room temperature under solvent condition. *Synth. Commun.* **2008**, *38*, 2103–2112.
17. *European Pharmacopoeia*, 7th ed.; European Directorate for the Quality of Medicines (EDQM): Strasbourg, France, 2010; pp. 1924–1925.