Received: 18 March 2021 | Revised: 19 April 2021 | Accepted: 21 April 2021

DOI: 10.1002/jhet.4281

ARTICLE

JOURNAL OF HETEROCYCLIC CHEMISTRY WILEY

Synthesis and characterization of potential impurities of Oxcarbazepine drug substance: An antiepileptic agent

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Abstract

Oxcarbazepine is a drug substance used to treat epilepsy. During its bulk synthesis of various impurities formation will be observed. Herein we describe the formation, synthesis and characterization of four potential impurities, namely, *N*-acetyl Oxcarbazepine, *N*-formyl Oxcarbazepine, *N*-carbamoyl Oxcarbazepine, and Oxcarbazepine dimer. These impurities are listed in several Pharmacopoeias and the control of these impurities below the threshold level is essential. Our study will be a guide for making these reference standards.

KEYWORDS

Oxcarbazepine dimer, Oxcarbazepine enamine, Oxcarbazepine impurities, Oxcarbazepine impurity D

1 | INTRODUCTION

Oxcarbazepine **1** (Figure 1) is an established agent used in the treatment of tonic-clonic seizures or partial epilepsy, trigeminal neuralgia, and affective disorders [1–5]. Oxcarbazepine is used alone or in combination with other medications for the treatment of focal (partial) seizures in adults [6–8]. In pediatric populations, it can be used by itself for the treatment of partial seizures for children 4 years and older, or in combination with other medications for children 2 years and older [9]. Oxcarbazepine is a prodrug, which is largely metabolized to its pharmacologically active 10-monohydroxy derivative licarbazepine [6].

Oxcarbazepine was patented in 1969 and entered the market in 1990 [10,11]. It is available as a generic medication from 2017, it was the 207th most commonly prescribed medication in the United States, with more than 2 million prescriptions [7]. The recommended dosage is as monotherapy for adults with epilepsy is 600–1200 mg orally per day, generally in three divided doses [11].

Oxcarbazepine is chemically known as 10,11-dihydro-10-oxo-5*H*-dibenz[b,f]azepine-5-carboxamide [7] or 10-oxo-10,11-dihydro-5*H*-dibenzo[b,f] azepine-5-carboxamide [8]. Oxcarbazepine is sold under the brand name Trileptal.

Understanding the related substances and its impact on the drug product stability is essential in designing and developing a robust drug product. International Conference on Harmonization defines impurity as any component present in the drug substance that is not a drug is treated as an impurity. Impurities will play a pivotal role in safety and toxicological properties of a drug substance. One of the major challenges for an organic chemist working in API industry is to synthesize and characterize critical impurities. There is very limited literature available for the synthesis of impurities [12].

The specification for Oxcarbazepine (**1**) is designed to control the identity, purity, and impurities arising from the manufacturing process and to reflect the compliance with US Pharmacopeia and European Pharmacopeia. As per the US Pharmacopeia (USP 40), the threshold limit of specified or unspecified limit of Oxcarbazepine should be <0.10%. We have synthesized and characterized

four impurities, namely *N*-acetyl Oxcarbazepine (**2**) *N*-carbamoyl Oxcarbazepine (**3**) *N*-formyl Oxcarbazepine (**4**) and Oxcarbazepine Dimer (**5**). The present article describes the investigations on the synthesis and structural characterization of these impurities.

2 | RESULTS AND DISCUSSION

Oxcarbazepine (**1**) is a second generation drug of the dibenz[b,f]azepine family and used in the treatment of epilepsy, trigeminal neuralgia, and AIDS-related neural disorders [13,14]. Most possible synthesis of Oxcarbazepine (**1**) is from commercially available 10-methoxy-5*H*-dibenzo [b,f]azepine or 10-methoxy iminostilbene (**6**) as shown in Scheme 1. Additionally, numerous synthetic methods are well documented in the literature for Oxcarbazepine (**1**) [15–17].

Oxcarbazepine is listed drug in US Pharmacopoeia and European Pharmacopoeia. During the manufacturing of Oxcarbazepine, the following impurities were described as potential impurities in US Pharmacopeia as shown in Figure 2. These impurities are required in quantities as impurity standards. Based on the significance of these impurities, we describe the simple and convenient synthetic protocols of four potential impurities (**2**, **3**, **4**, and **5**) from commercially accessible raw materials.

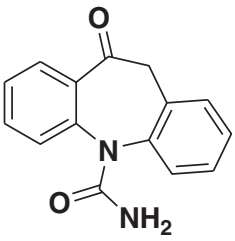


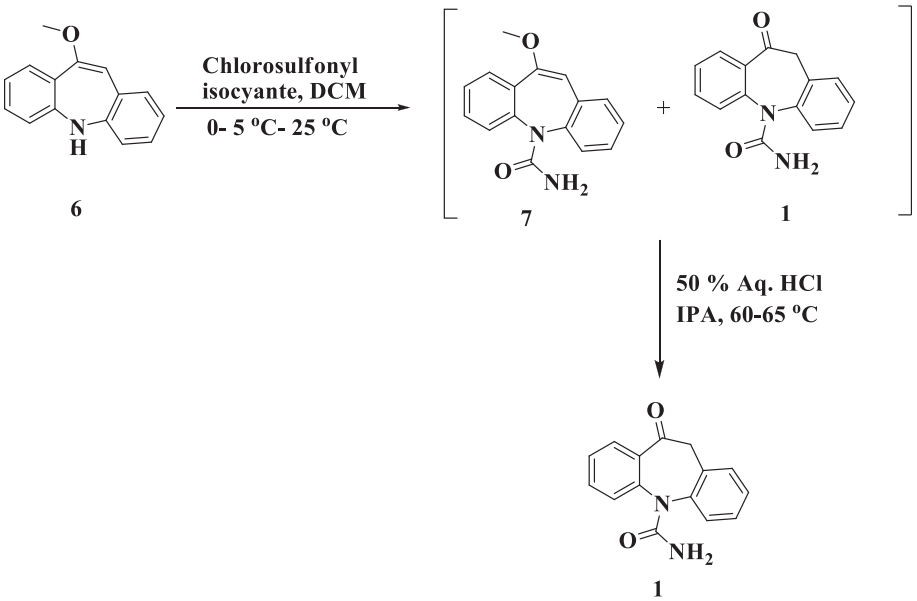
FIGURE 1 Chemical structure of Oxcarbazepine **1**

2.1 | Preparation of *N*-acetyl Oxcarbazepine (2)

N-acetyl Oxcarbazepine (**2**) impurity is listed as impurity-L in European Pharmacopeia. During the manufacturing of **1** via Carboxamidation of 6. Acetylation with traces of acetic acid present in the manufacturing process results in the formation of **2**. To prepare this impurity, an independent synthesis was carried out by reacting Oxcarbazepine enol acetate **8** with acetyl chloride in the presence of sodium hydride as a base (Scheme 2). Oxcarbazepine exhibits keto enol tautomerism. Due to this, when we perform acetylation on Oxcarbazepine, it results in the formation of Oxcarbazepine enol acetate 8 [18,19].

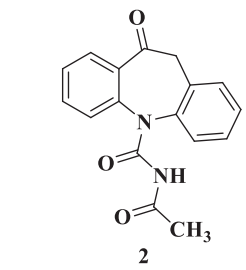
2.2 | Preparation of *N*-carbamoyl Oxcarbazepine (3)

Quite frequently, carboxamidation of **6** lead to the formation of **7** and further carboxamidation reaction on **7** gives **3**. Thus, *N*-Carbamoyl Oxcarbazepine (**3**) was prepared by reacting Oxcarbazepine with chlorosulfonyl isocyanate in DCM at lower temperature, as shown in Scheme 3.



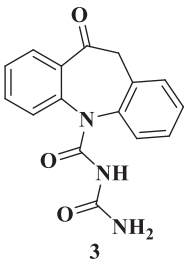
SCHEME 1 Reported synthesis of Oxcarbazepine (**1**)

FIGURE 2 Chemical structures of impurities



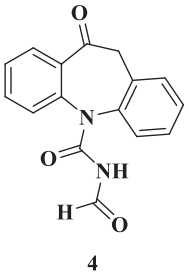
2

***N*-Acetyl Oxcarbazepine (or) Oxcarbazepine Related Compound B (or) Ph.Eur. Impurity L**



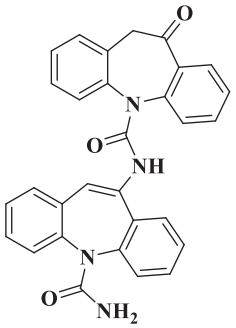
3

***N*-Carbamoyl Oxcarbazepine (or) *N*-carbamoyl-10-oxo-10,11-dihydro-5*H*-dibenzo[b,f]azepine-5-carboxamide**



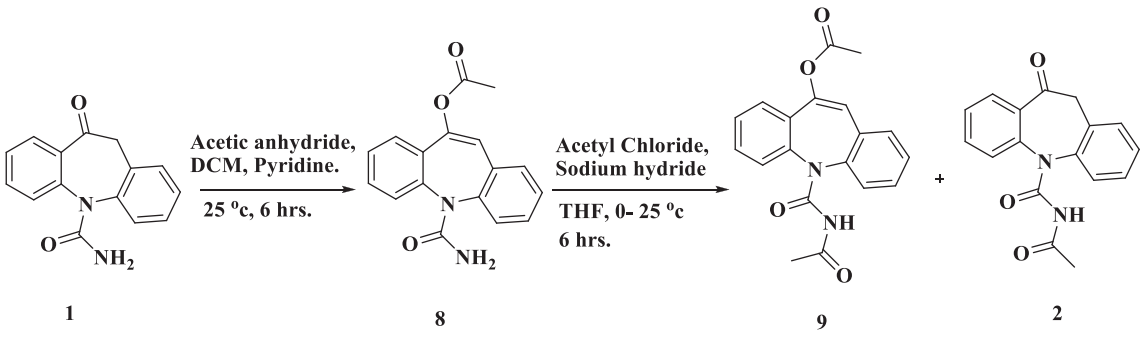
4

***N*-Formyl Oxcarbazepine (or) Oxcarbazepine Related Compound A (or) Ph.Eur. Impurity K**

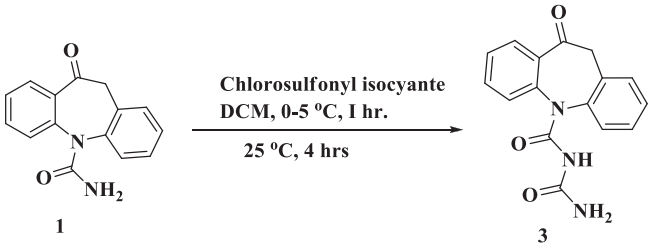


5

Oxcarbazepine Dimer (or) Oxcarbazepine Related Compound D (or) Ph.Eur. Impurity M



SCHEME 2 Synthesis of *N*-acetyl Oxcarbazepine (**2**)



SCHEME 3 Synthesis of *N*-carbamoyl Oxcarbazepine (**3**)

2.3 | Preparation of *N*-formyl Oxcarbazepine (4)

The presence of formic acid in the manufacturing process of **1** via carboxamidation of **6** followed by hydrolysis of **7** leads to the formation of **4**. *N*-formyl Oxcarbazepine (**4**) was prepared by reacting Oxcarbazepine (**1**) in a mixture of acetic anhydride and formic acid, as shown in Scheme 4.

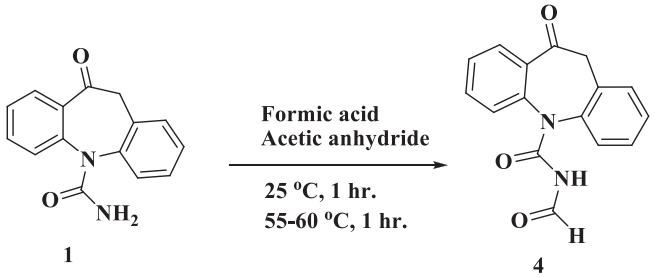
2.4 | Preparation of Oxcarbazepine dimer (5)

This dimer impurity forms by dehydration during dimerization. The plausible mechanism for the formation of Oxcarbazepine dimer impurity is described in Figure 3.

A series of attempts were made for the synthesis of Oxcarbazepine enamine (**10**), it was quite challenging to synthesize Oxcarbazepine enamine in pure form with good yield. We were successful in making Oxcarbazepine enamine when we performed the reaction in an

autoclave by treating Oxcarbazepine with titanium isopropoxide in the presence of ammonia gas and using ethanol as a solvent. Optimization conditions are mentioned in Table 1.

Another challenge posed to us was coupling of Oxcarbazepine enamine with dibenzazepino carbonyl chloride, several series of reactions with various base and solvent combinations were performed namely, Sodium hydride and DMF, Triethylamine, and DCM, Potassium carbonate and DMF, and so forth finally we have succeeded in dimer synthesis by reacting Oxcarbazepine enamine (**10**) with Dibenzazepino carbonyl chloride (**12**) in the presence of pyridine in DCM as shown in Scheme 5.



SCHEME 4 Synthesis of *N*-formyl Oxcarbazepine (**4**)

3 | CONCLUSION

Related substances or degradation impurities in drug products are controlled by pharmaceutical industries depending upon their acceptance criteria and regulatory guidelines. In this article, four listed pharmacopoeial impurities have been discussed. Chemical synthesis of these impurities along with their origin has been described. These impurities are of great importance to monitor their acceptance criteria in Oxcarbazepine drug product-related substances analysis.

4 | EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded by Bruker Avance 300 MHz and Varian 500 MHz using TMS as

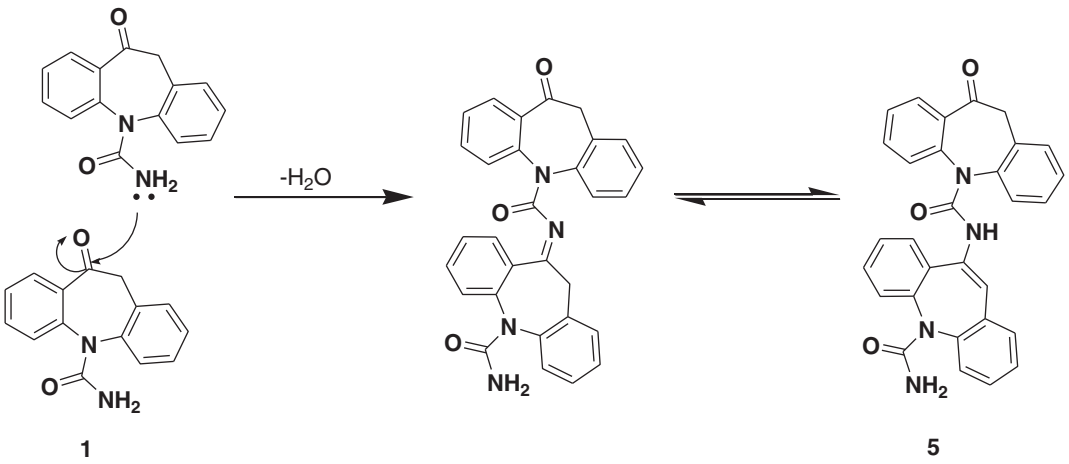
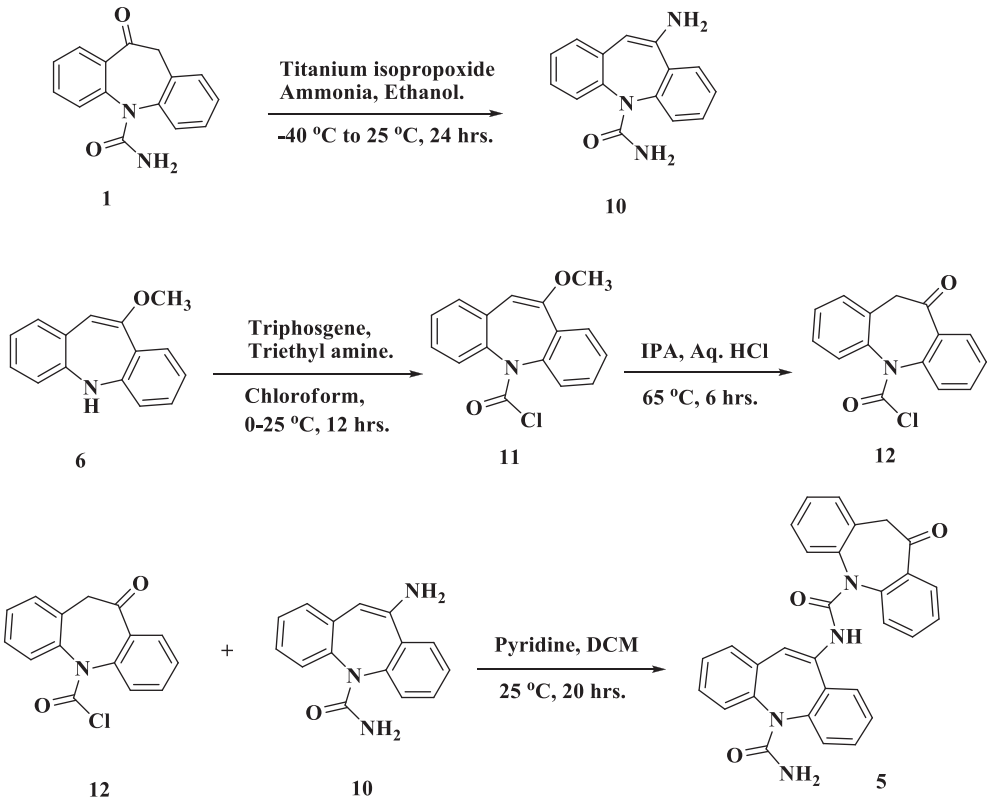


FIGURE 3 Plausible mechanism for the formation of Oxcarbazepine dimer (**5**)

TABLE 1 Optimization conditions for the synthesis of Oxcarbazepine enamine

S. no	Reagents	Conditions	Yield
1	Oxcarbazepine (1 mole), Titanium isopropoxide (0.2 moles) and 20% Ethanolic ammonia (8 moles)	0°C to 25°C, 10 h	No reaction
2	Oxcarbazepine (1 mole), Titanium isopropoxide (0.2 moles) and 20% Ethanolic ammonia (8 moles)	−20°C to 5°C, 5 h	5%
3	Oxcarbazepine (1 mole), Titanium isopropoxide (0.2 moles) and Ammonia gas (8 moles)	−20°C to 5°C, 5 h	7%
4	Oxcarbazepine (1 mole), Titanium isopropoxide (0.2 moles) and Ammonia gas (8 moles)	−20°C to 5°C, 5 h and 5°C to 25°C in an Autoclave for 24 h.	80%

SCHEME 5 Synthesis of Oxcarbazepine dimer (**5**)



internal standard. The chemical shift values were reported in the δ scale to TMS (δ 0.00) and the chemical shift values were given relative to D_2O, $CDCl_3$ and DMSO d-6 as internal standards. The IR spectra were recorded as KBr pellets using Perkin Elmer spectrophotometer. High-resolution mass analysis was done using electro spray ionization method and a Xevo G2 QTOF mass spectrometer. All raw materials were purchased from commercial sources and used without purification (Data S1).

4.1 | Synthesis of *N*-acetyl Oxcarbazepine (2)

Oxcarbazepineenol acetate [18,19] (30 g, 0.11 mol) was dissolved in THF (300 ml) at 25°C in the presence of nitrogen. Fifty percentage Sodium hydride (9.8 g, 0.20 mol) was added in small portions at 0–5°C and the reaction mass was stirred for 30 min. Acetyl chloride (8 g, 0.10 mol) was added to the reaction mass drop wise for a period of 15 min. The reaction mass was allowed to stir at 25°C for 6 h. After completion of the reaction, monitored by TLC, saturated aqueous ammonium chloride solution was added slowly to the reaction mass. The reaction mass was extracted with ethyl acetate, (2 × 300 ml). The combined organic extract was dried over sodium sulphate, concentrated to obtain a residue, which was chromatographed over 100–200 mesh size silica to obtain white solid of title compound (1 g). A mixture of 50% ethyl acetate and hexane was used as a mobile phase to elute pure compound. ^{1}H NMR (300 MHz, $CDCl_3$): 2.53 (s, 3H), 3.88 (d, 1H), 4.37 (d, 1H), 7.37–7.63 (m, 8H), 8.15 (d, 1H); ^{13}C NMR (75 MHz, D.M.S.O) 38.66–40.33, 104.01, 126.76, 127.32, 127.71, 127.86, 128.34, 129.49, 132.89, 133.89, 140.96, 143.25, 151.40, 170.70, 192.31; IR (KBr): 3455, 3340, 2717, 1946, 848 cm^{-1}; HRMS (ESI-QTOF) for $C_{17}H_{14}N_2O_3$ $[M + H]^+$: m/z calcd:295.1082; found:295.1076.

4.2 | Synthesis of *N*-carbamoyl Oxcarbazepine (3)

To a stirred suspension of Oxcarbazepine (5 g, 0.01 mol) in DCM (50 ml), chlorosulfonyl isocyanate, (4.3 g, 0.03 mol) was added dropwise for 15 min at 0–5°C. The reaction mass was allowed to stir at 0–5°C for 1 h. After completion of the reaction, monitored by TLC, glacial acetic acid (15 ml) and cold water (10 ml) were added. The reaction mass was stirred for 4 h at 25°C. The reaction mass was extracted with DCM (2 × 100 ml). The combined organic extract was dried over sodium sulphate and concentrated to obtain a residue. This residue was purified by column chromatography using 100–200 mesh size silica as stationary phase and a mixture of 1% ethyl acetate in methanol as mobile phase to afford

N-carbamoyl Oxcarbazepine as a pale yellow solid (1 g). ^{1}H NMR (500 MHz, DMSO-d_6): 3.80 (d, 1H), 4.45 (d, 1H), 7.15 (brs, 1H), 7. 48 (brs, 1H), 7.33–7.67 (m, 7H), 7.94 (d, 1H), 8.27 (brs, 1H); ^{13}C NMR (75 MHz, D.M.S.O) 38.65–40.32, 48.30, 103.82, 126.96, 127.57, 128.14, 129.72, 130.00, 130.55, 132.74, 133.46, 134.08, 134.93, 140.42, 142.61, 152.56, 153.77, 192.12;IR (KBr): 3488, 3227, 2924, 1959, 852 cm^{-1}; HRMS (ESI-QTOF) for $C_{16}H_{13}N_3O_3$ $[M + H]^+$: m/z calcd: 296.1034; found:296.1038.

4.3 | Synthesis of *N*-formyl Oxcarbazepine (4)

Formic acid (24 g, 0.048 mol) was added drop wise to acetic anhydride (44 g, 0.43 mol) at 25 °C for 20 min. This reaction mass was heated to 45–50°C and stirred for 1 h. The reaction mass was cooled to 25°C, Oxcarbazepine (12 g) was added and the reaction mass was heated to 55–60°C and stirred for 1 h. After completion of the reaction (monitored by TLC), the reaction mass was cooled and quenched with DM water. The precipitated product was extracted with ethyl acetate (3 × 300 ml). The combined organic extract was washed with DM water, dried over sodium sulphate and concentrated to obtain a residue. This residue was purified by column chromatography (100–200 mesh size silica) using a mixture of 40% ethylacetate and hexane as mobile phase to afford *N*-formyl Oxcarbazepine (3.5 gm) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): 3.89 (d, 1H), 4.36 (d, 1H), 7.33–7.66 (m, 8H), 8.14 (s, 1H), 8.98 (d, 1H), 9.15 (d, 1H); ^{13}C NMR (75 MHz, D.M.S.O) 38.66–39.77,126.73, 127.76, 128.10, 129.72, 133.18, 134.15, 140.35, 142.13, 152.08, 154.17, 192.28; IR (KBr) 3384, 3341, 1975, 1945, 1838, 830 cm^{-1}; HRMS (ESI-QTOF) for $C_{16}H_{12}N_2O_3$ $[M + H]^+$: m/z calcd: 281.0926; found: 281.0931.

4.4 | Synthesis of Oxcarbazepine dimer (5)

Oxcarbazepine enamine [20] (**10**) (1.8 g, 0.007 mol) was suspended in dichloromethane (30 ml). Pyridine (0.01 mol) was added to the reaction mass and stirred for 10 min at 25°C. To this reaction mass, dibenzazepino carbonyl chloride (**12**) (2.3 g, 0.0084 mol) was added at 25°C. The reaction mass was stirred for 20 h at 25°C. The reaction mass was quenched with water, extracted with ethyl acetate. The combined organic extract was concentrated to obtain a residue. This residue was purified by column chromatography (100–200 mesh size silica) to afford oxcarbazepine dimer (**5**) as a colorless solid (1 g). ^{1}H NMR (300 MHz, DMSO-d_6): 3.90 (m,1H), 4.48 (m, 1H) (5.45 (brs, 2H), 7.05–8.50 (m, 18H); ^{13}C NMR(75 MHz, D.M.S.O) 38.66–40.23, 126.87, 127.01, 127.46, 128.76. 129.56, 129.73, 134.03, 141.27, 156.07, 192.38; IR(KBr) 3645, 3626, 2924, 1131, 1036, 1021, 882, 668 cm^{-1}; HRMS (ESI-QTOF) for $C_{30}H_{22}N_4O_3$ $[M + H]^+$: m/z calcd: 487.1769; found: 487.1767.

ACKNOWLEDGMENTS

Our heartfelt gratitude to Dr. Syam Kumar U. K for his constant support and guidance for this work. The authors are grateful to the management of Aurobindo Pharma Ltd., for supporting this work. co-operation from colleagues of Chemical Research Department and Analytical Research department is highly appreciated.

DATA AVAILABILITY STATEMENT

Full Experimental details, 1H NMR spectra, 13C NMR spectra, FTIR and HRMS data can be obtained via the "Supplementary Content" section of the article's web page.

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Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: S. R. K. Velugula, A. S. K. Reddy, N. C. Misra, P. S. Reddy, R. Chavakula, A. K. Guduri, P. DouglasSanasi, *J Heterocyclic Chem* **2021**, 1–7. https://doi.org/10.1002/jhet.4281