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Review Article

MECHANISM OF ACTION, SYNTHESIS, PROPERTIES AND ANALYTICAL METHODS OF CABOZANTINIB

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ABSTRACT

Globally, the burden of cancer is substantial and growing. The impact of the burden of such diseases over society is unpredictable in terms of health lost and cost. Unfortunately, the estimates shown the burden may be increasing in the upcoming decades. Cabozantinib (CBZ) is a newly developed tyrosin kinase inhibitor (TKI) for Differentiated thyroid cancer (DTC), Hepatic Cellular Carcinoma (HCC), Medullary thyroid cancer (MTC) and Renal Cell Carcinoma (RCC). The objective of the presented review is to provide updated knowledge of drugs especially covering analytical methodologies. The review covered the introduction, mechanism of action, pharmacokinetics, synthesis and developed analytical methods by various researchers. The review covered one spectrophotometry and about twenty chromatography methods. The review will be helpful for the scientist working in this area and especially helpful for analytical scientists exploring new analytical methodologies for CBZ.

Keywords: Cabozantinib, Cancer, Analytical methods, Spectrophotometry, Chromatography

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INTRODUCTION

Cancer is the subsequent driving reason for death around the world [1], representing almost 10 million deaths in 2020 [2]. Cancers have tormented multicellular living creatures for more than 200 million years [3]. The circumstance is disturbing to such an extent that each fourth individual is having a lifetime chance of disease [4]. By 2040, the quantity of new patient growth cases every year is supposed to ascend to 29.5 million and the quantity of disease-related passings to 16.4 million [5]. Albeit the full degree of the effect of the COVID-19 pandemic in various world districts is right now obscure, defers in finding and therapy related with the worries of people, health system closures, including suspension of screening programs, and decreased accessibility of and admittance to mind are supposed to cause a transient decrease in disease rate followed by expansions in advanced stage diagnosis and cancer mortality in certain settings [6].

MTC occurs in both sporadic and heritable forms and is an aggressive form of thyroid cancer. Among all thyroid cancers, MTC prevalence is about 5 to 10%. MTC originate in the neural crest, emerges from the thyroid gland's parafollicular C cells. The disease advances from C cell hyperplasia (CCH), frequently with raised calcitonin levels, to microscopically invasive carcinoma, then grossly evident carcinoma [7]. The patient with localized disease and patients in regional stage illness have 95% and 75% overall survival (OS) rate, respectively. Just 20% of patients survive 10 y with diagnosed distant metastases which is fundamentally lower than for DTCs [8].

RCC originates from renal epithelium cells and records for over 90% of renal cancers. About 2% of all cancer diagnoses and cancer deaths worldwide are due to RCC with prevalence rates generally higher in developed countries [9]. Medullary thyroid cancer (MTC) is a rare cancer which occurs sporadically in almost 75% of cases or as inherited autosomal dominant syndromes originating from thyroid gland's parafollicular C cells [10]. Approximately 14% thyroid malignancy-related deaths are due to MTC accounting for 2% prevalence of all thyroid cancers. The survival rate is higher as compared to other cancers and the 10-year survival rate is 96% for benign thyroid cancer and 40% for malignant tumours [11].

HCC is a frequent type of liver cancer, which is the third driving reason for death due to cancer across the world [12]. Chronic liver infections (Hepatitis B and Hepatitis C), autoimmune hepatitis, smoking, alcohol intake, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease and aflatoxins intake are the major reasons and risk factors for the occurrence of HCC in both developed and developing countries [13, 14].

Starting from the beginning of this thousand years, another class of anticancer medications plays acquired a significant part in the therapy of solid and haematological tumours: the small-molecule kinase inhibitors (SMKIs) [15]. Protein kinases have arisen as the main class of focuses in oncology drug discovery on account of their significant jobs in controlling cell development and endurance. Therapy of these tumors with MET inhibitors brings an about dramatic response like massive apoptosis or proliferative block [16].

Cabozantinib (CBZ), an orally bioavailable small molecule [17], a tyrosine kinase inhibitor(TKI), [18] has been approved for the treatment of DTC, HCC, MTC and RCC [19]. CBZ's molecular formula ($C_{28}H_{24}FN_3O_5$), mol. wt. 501.5 and IUPAC name is "1-*N*-[4-(6,7-dimethoxyquinolin-4-yl)oxyphenyl]-1-*N*'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide" (fig. 1) [20]. CBZ is a BCS class II drug, having high permeability with low solubility and a weak base with pH-dependent solubility profile. CBZ is practically insoluble at pH>4 and in 0.01 N HCl, the solubility is 0.11 mg/ml (highest solubility at gastric pH). The dosing regimen for CBZ for MTC is 140 mg (capsules) administered orally OD, required no less than 1 h prior or 2 h after a food [21]. CBZ is available in the market as film coated tablets (Cabometyx, 60 mg) and capsules (Cometriq, 140 mg) formulations consisting of malate salt. Both the formulations differ in the rate of absorption and hence are not bioequivalent [22]. The most frequent adverse events (AEs) are fatigue, diarrhoea, hand-foot syndrome, hypertension, nausea, weight loss, and stomatitis [23].

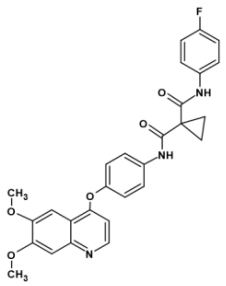

Fig. 1: Chemical structure of CBZ

For literature review, bentham, wiley, nature, springer, taylor and francis, oxford, hindawi databases were searched. Other than this, related articles were also searched in google. The keywords used were "Cabozantinib", "determination of cabozantinib", "analysis of cabozantinib", "mechanism of action of cabozantinib", and "green analytical methods".

Mechanism of action

A tumor can be defined as "A tumor (also called *neoplasm*) is an abnormal mass of cells in the body caused by cells dividing more than normal or not dying when they should" [24]. The tumor microenvironment is heterogeneous population of cells that respond to biological stimuli contributing to tumor growth. This dysregulated signalling of the cells can lead to abnormal cell growth and survival. Preclinical studies have shown that the dysregulated signalling of tyrosine receptor kinase (RTKs) such as AXL, MET and VEGFR play role in tumor cell proliferation, angiogenesis, and metastasis [25].

Receptor tyrosine kinases (RTKs) are known to be involved in both normal cellular function and pathological processes. Signalling of some RTKs such as MET, AXL and VEGFR also marginally modify the tumor response, which involves the activity of several immune cells, including dendritic cells, effector T cells and immunosuppressive cells e. g. regulatory T cells (Treg), Myeloid-derived suppressor cells (MDSC) and M2 tumor-associated macrophage [26].

The anti-tumor response may begin with dendritic cells capturing tumor-associated antigens and presenting them to T cells, which leads to T cell activation and proliferation. Activated T cells can infiltrate the tumor and promote T cell mediated killing of cancer cells. Inhibitory checkpoint proteins such as PD-1 and PD-L1, helps keeping immune system in check by preventing T cell activation; however, the tumor cells can exploit this mechanism by upregulated the checkpoints to invade immune detection [16]. In advanced renal cell carcinoma, the dysregulated signalling of MET, VEGFR and AXL can affect the entire tumor response in several ways including increase in immunosuppressive cells, decreasing antigen presentation, reducing cytotoxic T cells and T cells activation and reducing tumor recognition with an increase in PD1 and PD-L1 expression. The dysregulation of signalling of checkpoints together with MET, AXT and VEGFR, among other RTKs may help to hinder entire tumor immune response and contribute to tumour growth [27].

CBZ, a tyrosine kinase inhibitor that inhibits MET, AXL and VEGFR among other RTKs–"RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2" [28, 29]. The molecular docking studies published regarding interaction of CBZ with TAM kinases [30] is presented under fig. 2. This will further block the angiogenesis and cell proliferation of tumor and may also effect the microenvironment by reducing levels of immunosuppressive cells and by promoting its recognition by reducing immune checkpoints, increasing antigen presentation and increase in cytotoxic presentation and normalizing the vasculature to promote immune cell infiltration [31, 32].

CBZ, after oral administration, exhibits rapid absorption (C_{max} is achieved 3-5h post single oral dose) owing to its high permeability (BCS class II) [33, 34]. It exhibits long terminal t 1/2 (~ 120h) with high plasma protein binding (>99.7%). It endures wide distribution in various body tissues and has substantial metabolism as it is a substrate of Cytochrome P450, hence is vulnerable to drug-drug interaction [22, 35, 36]. Animal study suggests hepatobiliary excretion as a prime mode of elimination [36, 37]. In patients receiving CBZ diarrhea is the most usual adverse effect [33].

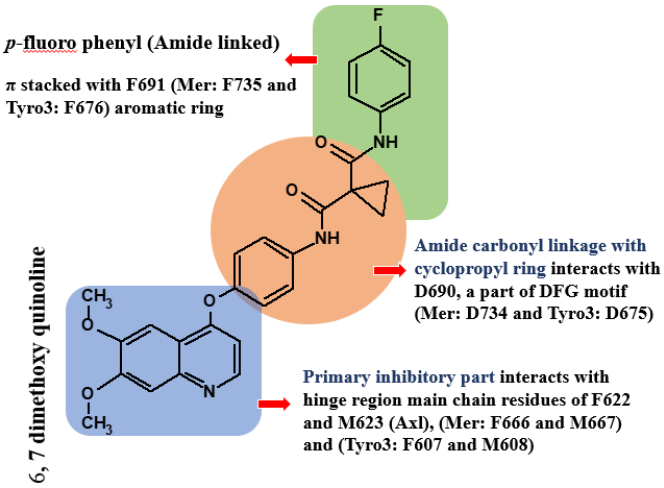

Fig. 2: Interaction of CBZ with TAM kinase receptors

Synthesis

There are published reports [38, 39] and patents [40-45] regarding the synthesis of CBZ (fig. 3). The key intermediate 6,7-dimethoxyquinolin-4-ol (4) (also highlighted in box), for the preparation of drug, can be synthesized by two different methods (as shown in Scheme 1, as Method A and Method B). In the method published by Fang *et al.* [39], a better alternative method for the preparation of key intermediate was proposed (Scheme 2) due to high reaction temperature requirement and the disadvantages of the Dowtherm A, such as high boiling point, difficulty in recovery and possible allergic reactions to workers, in previously published methods. In their method, the key intermediate (4) (also highlighted in box) was prepared from "1-(4,5-dimethoxy-2-nitrophenyl)-3-(dimethyl amino) prop-2-en-1-one" by reduced cyclization process (Scheme 2). The overall yield of the drug obtained after synthesis was 82%, as claimed by authors. There are few more methods for preparation reported with low yield of either key intermediate [40, 41] or the pure drug [42, 43]. The conversion of CBZ into salts (HCl and maleate) form is reported in the patents of MSN laboratories [44] and Natco pharma [45].

Analytical methods

Spectrophotometry

Spectrophotometry can be an expansion of any of the prior kinds of spectroscopy. A term alludes to the quantitative examination of spectra to compare the relative absorption or emission of light's different wavelengths [46]. Fluorescence occurs in simple as well as in liquid, complex gaseous, and chemical systems (solids). While fluorescence can be seen from all molecules with an "excitation beam in adequate intensity" just a little piece of particles exhibits fluorescence qualities which are attractive for scientific purposes. In this manner, fluorescence spectroscopy is less general than absorption procedures, even though it is more selective [47].

The micelle-enhanced spectrofluorimetric method of CBZ for determination in spiked human plasma and dosage form without any derivatization developed by Darwish *et al.* [48]. The wavelength selected was λ_{em} at 430 nm and λ_{ex} at 275 nm. The LOD value was 13.34 ng/ml is lower than many of the published chromatographic methods. The method is based on the principle in the presence of Polyoxyl 40 hydrogenated castor oil (Cr RH 40), the native fluorescence of the drug in an aqueous solution increases to approximately nine folds. The NMR and IR spectrum are shown under fig. 5 and 6, respectively.

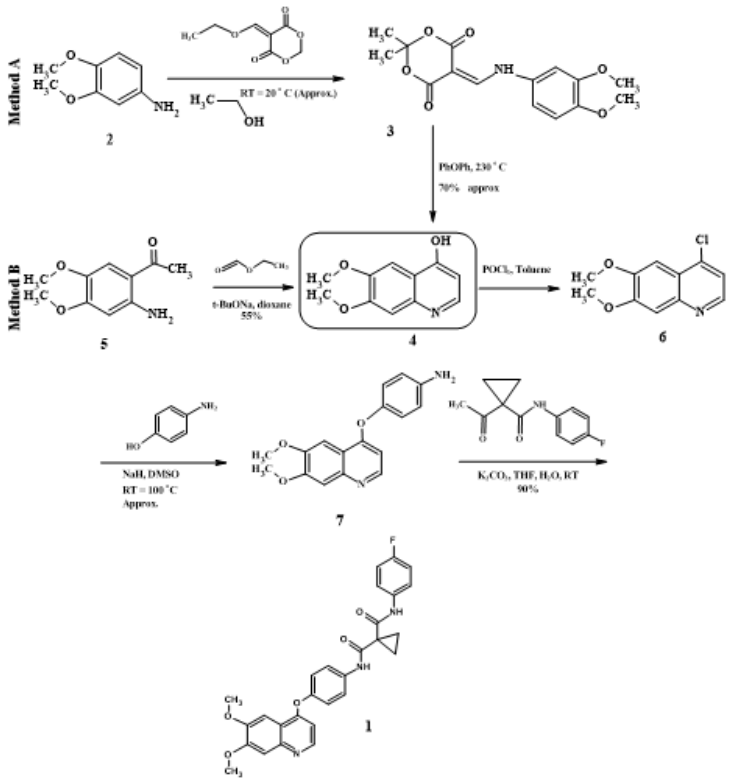

Fig. 3: Scheme of synthesis of CBZ (Scheme I)

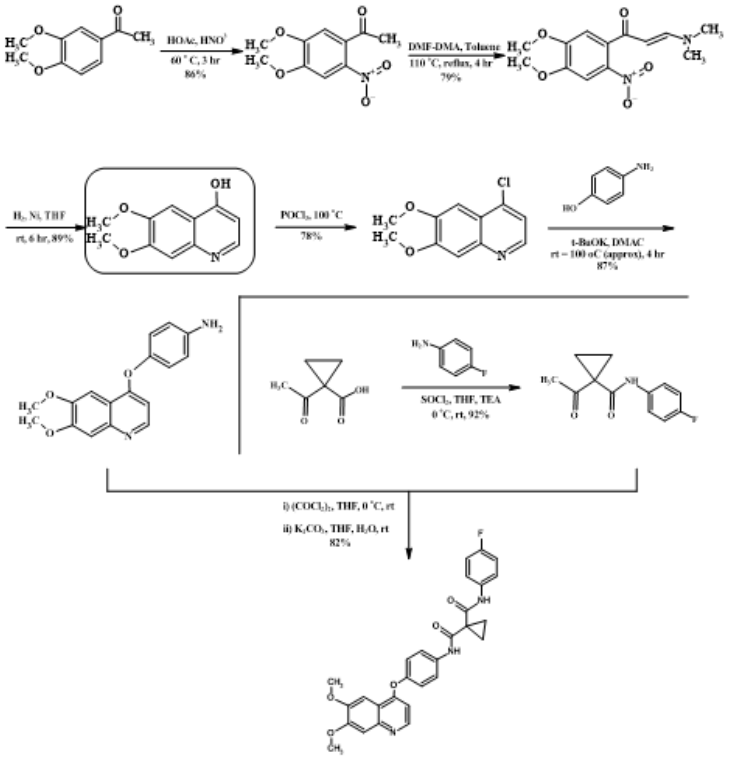

Fig. 4: Scheme for synthesis of CBZ (Scheme II)

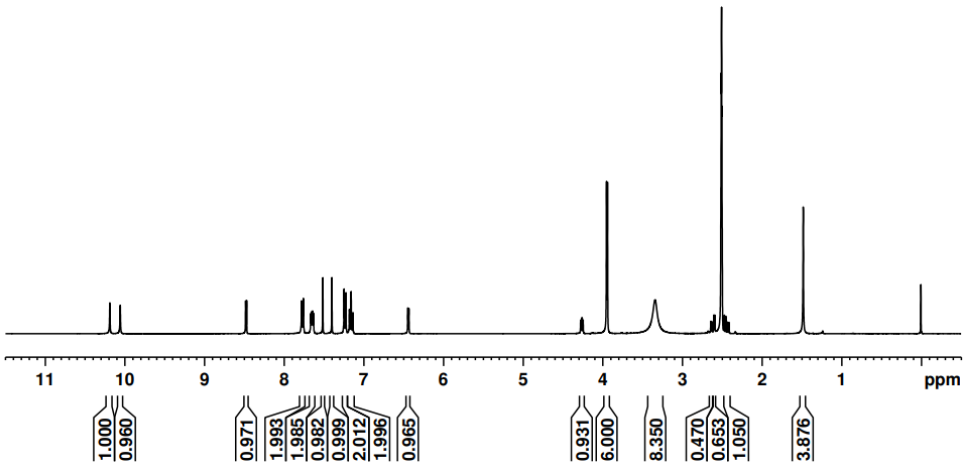

Fig. 5: NMR spectrum of CBZ

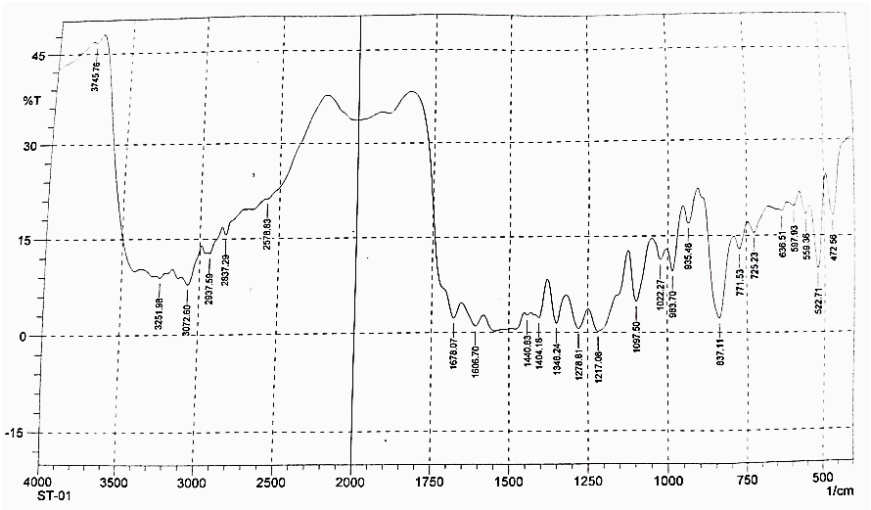

Fig. 6: IR spectrum of CBZ

Chromatography

With the advancement in separation science, chromatography methods along with modern detectors are widely used for the analysis of simple to complex matrices because of more selectivity and sensitivity [49, 50]. The summary of chromatography methods is provided under table 1.

Table 1: Summary of chromatography methods

Method	Column	Detector	Mobile phase	Elution	Linear range	LOD	LOQ	Applications	References
LC	C_{18} (4.6 mm × 250 mm, 5 µm), 40 °C,	TOF-MS MS/MS	ACN: CH_3COONH_4 buffer (20 mmol), 57:43 (v/v) at 1.0 ml/min	Isocratic	0.05-60 µg ml^{1}	0.01 µg ml^{1}	0.05 µg ml^{1}	Forced degradation and degradation kinetics	[51]
UPLC	C_{18} (2.1 mm × 100 mm, 1.7 µm	MS/MS	ACN and water (+0.1% formic acid)	Gradient	5–5000 ng/ml	-	-	Pharmacokinetics and tissue distribution in rat	[52]
LC	C_{18} column (50 × 2 mm, 5 µm)	MS/MS	ACN-H_2O (45:55, v/v), 5 mmol NH_4HCO_2 buffer (pH adjusted to 5), 0.4 ml/min	Isocratic	0.5–1000 ng/ml	-	0.5 ng/ml	Rat plasma	[53]
LC	-	MS/MS	-	-	0.5-400 ng/ml	-	0.5–1 ng/ml	Pharmacokinetic drug interaction studies	[54]
LC	-	MS	-	-	0.5-400 ng/ml	-	0.5 ng/ml	Effect of gastric pH and food on	[55]

Method	Column	Detector	Mobile phase	Elution	Linear range	LOD	LOQ	Applications	References
								pharmacokinetics	
LC	C_{18} (50 mm × 2.0 mm i.d., 3.0 µm)	MS	ACN: 0.01 M NH_4HCO_2 buffer (pH 4.1), 50:50, 0.3 ml. min^{-1}	Isocratic	1.0-100 ng ml^{1}	0.29 ng ml^{1}	0.91 ng ml^{1}	Simultaneous estimation with tofacitinib and afatinib in human plasma and urine	[56]
LC	50 mm × 2.0 mm i.d., 3.0 µm	MS/MS	ACN: 0.01 M NH_4HCO_2 buffer (pH 4.1), 50:50, 0.3 ml. min^{-1}	Isocratic	2.5-100 ng ml^{-1}	0.32 ng ml^{1}	0.97 ng ml^{1}	Simultaneous determination with other five tyrosine kinase inhibitors in human plasma	[57]
UPLC	C_{18} (100 mm × 2.1 mm, 1.7 µ)	UV, 244 nm	0.1% H_3PO_4 and ACN (55:45%v/v), column temp. 30 °C 0.3 ml/min.	Isocratic	20–120 µg/ml	0.15 µg/ml	0.17 µg/ml	Stability-indicating method	[58]
LC	C_{18} column (2.1×150 mm, 3 µm)	MS-MS	ACN: 10 mmol CH_3COONH_4 (+0.1% HCOOH) (78:22, v/v), 0.3 ml/min	Isocratic	0.500-5000 ng/ml	-	0.5 µg/ml	simultaneous determination with cabozantinib N-oxide (metabolite)	[59]
LC	C_{18}, 50 × 4.6 mm, 5 µm	MS-MS	10 mmol CH_3COONH_4:Methanol, 20:80 v/v, 0.7 ml/min	Isocratic	5.0-5000 pg/ml	50 pg/10 µl	5 pg/ml	Human plasma	[60]
LC	C_{18} 150 × 4.6 mm, 5µ	UV, 210 nm	KH_2PO_4 Buffer and ACN (55:45% v/v), 1.0 ml/min	Isocratic	5-30 µg/ml	0.03 µg/ml	0.10 µg/ml	API and dosage forms	[61]
LC	C_{18} column (150×4.6 mm, 3.5µ)	UV, 219 nm	0.1% TEA: ACN, (70:30), 1 ml/min	Isocratic	1-20µg/ml	0.1 µg/ml	1 µg/ml	Rat plasma	[62]
UPLC	C_{18} Column (2.1 × 50 mm, 1.6 µm)	MS-MS	A: 0.1% HCOOH in water, B: 0.1% HCOOH in ACN	Gradient	6-1,000 µg/l	-	99.9 µg/l	Simultaneous determination-cobimetinib, cabozantinib, dabrafenib, niraparib, olaparib, vemurafenib, regorafenib and its metabolite regorafenib M2	[63]
MLC	C_{18} 100 A°	Fluorescence (Ex: 245–295, Em; 342–483 nm	ACN, CTAB (0.2 mol. L^{-1}), and tris buffer (pH 8.5), 40:50:10 (v/v) ratio.	Isocratic	20 to 700 ng. ml^{1}	2.11 ng. ml^{1}	20 ng. ml^{1}	CBZ and main metabolites	[64]
HPLC	C_{18}, 4.6 × 250 mm, 5 µm	UV, 244 nm	MeOH: phosphate buffer (pH. 3.00), (55:45 % v/v), flow rate, 0.8 ml/min	Isocratic	10 60 µg/ml	0.2085 µg/ml	0.6321 µg/ml	API and dosage form	[65]
RP-HPTLC	RP-18 silica gel 60 F_{254S} plates	247 nm	acetone/water 85:15, vv^{-1}	-	10–1000 ng $band^{-1}$	3.42±0.10 ng $band^{-1}$	10.26±0.30 ng $band^{-1}$	tablets and capsules	[66]
NP-HPTLC	NP-18 silica gel 60 F_{254S} plates	247 nm	Ethyl acetate/ethanol, 97.5:2.5, $v\ v^{-1}$	-	50–600 ng $band^{-1}$	17.01±0.26 ng $band^{-1}$	51.03±0.78 ng $band^{-1}$		
LC	150×4.6 mm, 3.5 µm	UV, 222 nm	0.1% TEA: ACN (70:30), 1 ml/min	Isocratic	6-90 µg/ml	0.075µg/ml	0.248µg/ml	Simultaneous determination with Nivolumab	[67]
LC	C_{18}, 150×4.6 mm, 3.5 µ	UV, 216 nm	0.1 % H_3PO_4: ACN	Gradient	20 to 300 µg/ml	0.2 µg/ml	2 µg/ml	Assay, related substances and dissolution studies	[68]
LC	2.1 mm × 100 mm, 3.5 µ	MS-MS	0.2% HCOOH: ACN (40:60 v/v), 0.12 ml/min	Isocratic	5 ng/ml to 75 ng/ml	1.5 ng/ml	5 ng/ml	Dosage form	[69]

DISCUSSION

The development of a suitable analytical method is one of the critical steps in drug development [70-74]. The CBZ is no exception, and following discussion is regarding the different analytical methods available for its determination in different matrices.

Stability indicating methods

The LC/TOF-MS and LC–MS/MS methods were the initial developed methods with an aim to examine the degradation kinetics of CBZ [51]. Oxidation and hydrolysis are the primary degradation pathways, as reported by researchers. The scheme of formation of oxidative degradation product (Imp-3) and hydrolysis products of acidic and alkaline stress conditions (Imp-1 and Imp-2) are shown in fig. 7. Forced degradation under extreme conditions was also utilized for the separation of potential degradants. The approach was used in the stability indicating method reported by Gojra *et al.* [58]. The retention time was just 1.3 min, but the structure of degradants was not reported.

UPLC methods

UPLC strategies are utilized over the HPLC techniques, as they give influence of time, endeavours, and saving resources [70]. Two methods based on UPLC gradient elution available. The first method by Wang *et al.* [52] is based on gradient elution in which ACN (95%) maintained for 0.5 min and kept up with at 20% for 0.4 min with 3 min total run time. Another method [63] is for the simultaneous determination of other six anticancer drugs with run time of 7 min. The gradient elution was performed using 0.1% HCOOH in water plus 0.1% HCOOH in ACN. The method, however, utilized more solvents but additional advantageous, particularly for those pharmaceutical companies producing more than one anticancer drug. Another stability-indicating method [58] based on isocratic elution UPLC method is also reported.

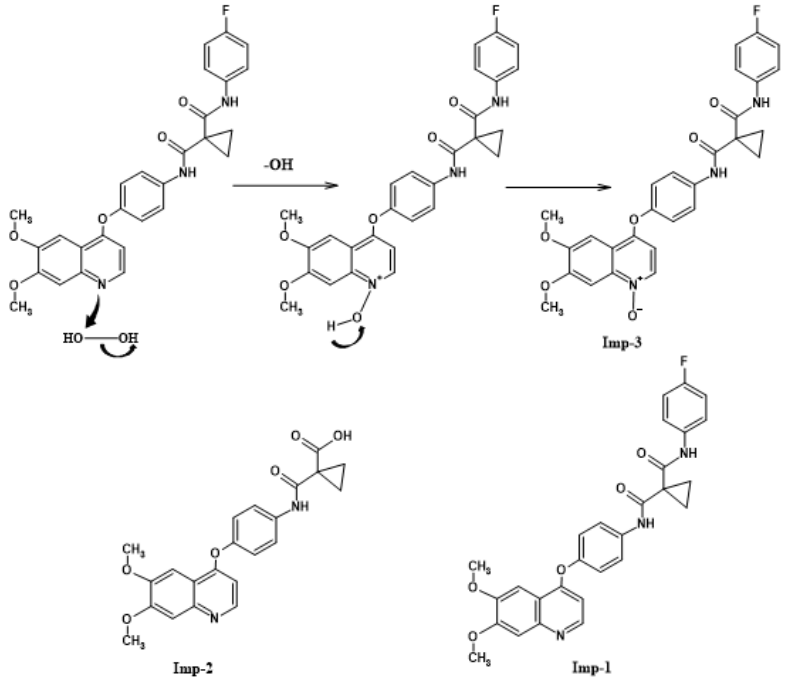

Fig. 7: The degradation products and impurities of CBZ

Pharmacokinetic studies

The pharmacokinetic and tissue distribution study of CBZ is published by Wang X *et al.* [52] compared four different dosages of the drug i.e., s (iv 5, 10 mg/kg and intragastric (ig) 15, 30 mg/kg) in four groups rats. They reported the elimination half-life ($t_{1/2}$) more than 10 h., possibly due to decrease in metabolic activity with the an increase in dosage and tissue distribution observed was liver>lung>kidney>spleen>heart. Another LC-MS/MS method aimed for pharmacokinetic study in in Sprague-Dawley rats, developed by Su Q *et al.* [53], using a single dose (0.5 mg/kg) of oral administration. The pharmacokinetics of CBZ was described by a two-compartment model with zero-order absorption.

The pharmacokinetic drug-drug interactions with rifampin and ketoconazole in healthy volunteers and rosiglitazone in patient with solid tumors were published by Nguyen *et al.* [54]. The plasma and urine samples were evaluated using LC-MS/MS method. The researchers reported an increased and decreased metabolism of CBZ with concomitant usage of rifampin and ketoconazole, respectively. There is no significant effect of steady-state concentration of CBZ on rosiglitazone metabolism.

The effect of food and pH on the bioavailability of CBZ was evaluated by Nguyen and co-researchers [55]. The plasma drug concentration was evaluated using LC-MS/MS method. The researchers concluded to avoid CBZ intake with food (to be taken on an empty stomach) and there is low risk of interaction with proton pump inhibitor esomeprazole. The primary oxidative (nonconjugated) metabolite is cabozantinib *N*-oxide is carcinogenic and mutagenic. The simultaneous method with the parent molecule was developed by Ren *et al.* [59], for the pharmacokinetic study in rats at different dosages.

Determination in marketed formulations

There are seven different methods [61, 65-69] with different applications like determination in API and/or dosage forms [61, 65-69], related substance [68], dissolution studies [68] or in combinations. The recently developed LC-MS/MS method [69] with LOD and LOQ of 1.5 ng/ml and 5 ng/ml, respectively, is the most sensitive method in this segment.

Green analytical method

Green analytical method energizes diminishing the utilization of harmful synthetics/reagents, utilizing energy-proficient equipment, and creating negligible waste. The new patterns in analytical strategy advancement center around the scaling down of the example readiness gadgets, the improvement of solventless or

dissolvable limited extraction methods, and the use of less harmful solvents [75, 76]. In the analytical method development of CBZ, the research published by Alam *et al.* [66] is the only direct attempt. In the RP-HPTLC method, green acetone/water (85:15, vv^{-1}) was used as mobile phase. For NP-HPLTC method, green ethyl acetate/ethanol (97.5:2.5, vv^{-1}) was utilized as the mobile phase.

The UPLC methods utilizes short column with low porosities and high pressure from pump allowed only minute volume of mobile phase passing through the line at a time. This not only minimizes the separation time but also reducing mobile phase volume which is mainly consisting of toxic or corrosive solvents. Thus, these methods also indirectly contribute to the green analytical chemistry approach.

CONCLUSION

Globally, the burden of cancer is substantial and growing. The ineffectiveness of drugs due to resistance is believed to be reason for the deaths up to 90% for cancer patients. The CBZ is one of the additions for therapy with potential antineoplastic activity. The advancement in the field of knowledge of targeted therapeutics for cancer treatment with drug development strategies may be one of the challenges for research scientists. The presented review is an attempt to support them in recent developments about CBZ. Currently, there is only one spectrophotometry method is available, which explores the opportunity to analytical scientists to develop the sensitive and simple method. There are many chromatography methods available, and a summary is presented under table 1. The incorporation of green analytical method concept is also one of the requirements to develop cost-effective, environmentally friendly analytical methods.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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