Importance of Fluorine in Benzazole Compounds

Thuraya Al-Harthy 1,* , Wajdi Zoghaib 2 and Raid Abdel-Jalil 2,*

1 Department of Basic Sciences, College of Applied and Health Sciences, A’Sharqiyah University, Ibra 400, Oman
2 Chemistry Department, College of Science, Sultan Qaboos University, Al-Khod, Muscat 123, Oman; zoghaibw@squ.edu.om

* Correspondence: thuraya.alharthy@asu.edu.om (T.A.-H.); jalil@squ.edu.om (R.A.-J.)

Academic Editor: Mohamed Abarbri
Received: 9 July 2020; Accepted: 18 September 2020; Published: 14 October 2020

Abstract: Fluorine-containing heterocycles continue to receive considerable attention due to their unique properties. In medicinal chemistry, the incorporation of fluorine in small molecules imparts a significant enhancement their biological activities compared to non-fluorinated molecules. In this short review, we will highlight the importance of incorporating fluorine as a basic appendage in benzothiazole and benzimidazole skeletons. The chemistry and pharmacological activities of heterocycles containing fluorine during the past years are compiled and discussed.

Keywords: benzazoles; benzimidazoles; benzothiazoles; benzoxazole; fluorine; biological activities

1. Introduction

Fluorine is one of the halogens located in the main group 7A of the periodic table of elements and it is the most electronegative element, with a Pauling assigned electronegativity value of χ = 4.0. The electronegativity leads to more polarization of C-F bond (µ C−F = 1.41 D), less covalent and more electrostatic character. Usually C–F bond does interact with its environment via electrostatic/dipole interaction. Fluorine has the smallest atomic radius among the Period 2 elements. Due to the relatively small size of fluorine compared to the hydrogen atom, it can closely mimic hydrogen in non-fluorinated analogues allowing a fluorinated precursor to fit in a given enzyme receptor and hence giving similar or enhanced biological activity. Although the carbon-fluorine bond is stronger (105.4 kcal mol\(^{-1}\)) than a carbon-hydrogen bond (98.8 kcal mol\(^{-1}\)) providing a higher thermal stability, yet fluorine is still a better leaving group than hydrogen. This review summarizes the literature data published in the last two decades and dealing with the biological impact of introducing fluorine as a major appendage of benzazoles. The biological activity of the most important representatives of this class of compounds are discussed.

1.1. Heterocycles in Medicinal Chemistry

Heterocycles are indispensable constituent molecules widely distributed in Nature and involved in many essential biomolecules. Heterocyclic organic compounds are involved in an exceptionally broad domain of reactions in Nature and their utility extends to different disciplines: like medicine [1], agriculture [2], industry and technology [3]. Fluorine was synthetically incorporated in many heterocycles in the 1970s and onwards when an appreciation of the significance of fluorine started to emerge in medicinal chemistry. Fluorinated compounds comprise about a quarter of commercially available drugs in the market [4]. The number of compounds containing fluorine has increased year by year during the past 50 years and the reputation of fluorine continues till today where among the 48 new approved drugs in 2019, there were 13-fluorine containing drugs. That is due to the unique features of fluorine, which are discussed later in details. In medicinal chemistry, since the journey of
drug development is long, challenging and risky, choosing the proper moiety is highly crucial and fluorine has become a popular moiety used in small molecules to affect the biological activity.

1.2. The Role of Fluorine in Medicinal Chemistry

The following are general properties of fluorine which are exploited in medicinal chemistry and drug discovery in particular: pKa, steric effects, lipophilicity, inductive effect, hydrogen bonding, and isosterism that will be discussed later.

Typically, fluorine substitution lowers the pKa of the nearby functionality in which protic groups become more acidic and basic groups become less basic. The pKa of an ionizable center of a drug molecule can alter its lipophilicity. The pKa can be tuned and this can manifest in the potency, selectivity, toxicity, as well as pharmacokinetic (PK) properties, which is things are manifested in absorption, distribution, metabolism, and excretion (ADME). Besides that, it can also play an important role in reducing the potential toxicity. Thus, understanding the effect of fluorine substitution on the lead compound facilitates the journey of development of therapeutic agents. In acyclic aliphatic amines, as the fluorine substitution increases, the pKa decreases. Generally, the length of the chain does not shift the pKa of the amine [5].

An attempt has been done by Fjelbye et al. to elucidate the effect of replacing a hydrogen atom with fluorine on the pKa and P-glycoprotein (Pgp)-mediated eflux for a series of phosphodiesterase type 9 (PDE9) inhibitors [6]. A harmonic trend has been noted in the pKa shift for the synthesized compounds 1 (Figure 1) after hydrogen–fluorine replacement. Consequently, these possibilities or limitations which are afforded by fluorine can be beneficial in drug discovery.

![Figure 1. Series of PDE9 inhibitors upon H/F exchange at x position.](image-url)

The aqueous solubility of a compound is essential in drug development whereby poor solubility affected the ADME sequence starting from the first step; poor solubility that lead to poor absorption even if the permeation rate is high. Poor solubility can be improved by increased fluorine substitution.

Lou’s research team [7] prepared the lead compound 2 which exhibits a selective Bruton’s tyrosine kinase (BTK) inhibition with reasonable biological activity with human whole blood (HWB) IC50 of 100 nM and poor aqueous solubility (0.6/2/3 µg/mL in water). They aimed to improve the aqueous solubility, which in turn increases the biological activity which is expected to lower the effective dose. They utilized the approach that replacement of C-H bond with a C-F bond is believed to increase the metabolic stability and improve membrane permeability of a particular compound. In addition, the incorporation of fluorine in small molecules imparts higher binding affinity. In another study [7], Lou et al. demonstrated that a rational fluorine scan can be utilized to measure the potency of a series of selective BTK inhibitors. The placement of fluorine at the optimal position can lead to favorable interactions with protein side chains. Several analogues a, b and c, fluorinated and non-fluorinated at different sites in compound 2 (Figure 2); were used to investigate the fluorine moiety that could result in favorable interactions with the BTK protein. A single modification in compounds 3 and 4 increases the potency up to 40- and 20-fold when compared with non-fluorinated analogues. They concluded from their investigation that the favorable interactions and impact are attributed uniquely to the fluorine moiety.
The fluorine influence on pKa has been studied systematically in order to improve pharmaceutical properties of a thrombin inhibitor by lowering the pKa. Upon fluorine substitution, the pKa follows the expected trend and the binding affinity against thrombin and trypsin (Ki) decreases as the pKa decreases. Utilizing the linear free energy relationships (LFERS) to find out the relationship between the binding affinity and pKa, it was revealed that the thrombin inhibition is more sensitive to pKa of the amidine functionality than the inhibition of trypsin [8].

Because of the favorable half-life of the fluorine isotope $^{18}\text{F}$ (109.8 min), it stands out as a unique atom which is used in positron emission tomography (PET). $^{18}\text{F}$ became a powerful tool used for detection of various cancer types [9–11]. Ojima has introduced fluorine into taxoid anticancer agents and studied their tumor-targeted drug delivery systems [12]. The 3′-difluorovinyltaxoids (5) possess an exceptional potency against human breast, ovarian, colon and pancreatic cancer cell lines three times higher in potency compared to that of paclitaxel against breast cancer cell lines MCF-7 (drug-sensitive) and a multidrug-resistant cell line NCI/ADR (drug-resistant) cancer cell lines respectively.

One of the most critical concerns in drug development is the metabolism that results in reduced potency, poor PK properties or bio-activation into reactive species. An effort was done by Wan et al. to develop a series of piperidine-based 11β-hydroxysteroid dehydrogenase type I (11β-HSD1) inhibitors that may be useful targets for diabetes and obesity treatment [13]. Their work focused on improving the metabolic stability of 11β-HSD1 inhibitors. Comparing between the two compounds, the fluorine substituted 6 and the unsubstituted piperidine 7 (Figure 4) the substitution of fluorine into compound 6 has a tremendous impact metabolic stability. Due to fluorine substitution, the mouse liver microsome half-life (MLM) increased by up to 5-fold.
In drug design, the most crucial properties that control membrane binding are the lipophilicity and the cross-sectional area. Thereby, fluorine is a good choice as a lipophilic moiety in modulating lipophilicity for bioactive compounds. Lipophilicity is often expressed as log P, the logarithm of the partition coefficient of a compound between octanol and water. It is inaccurate to generalize the fact that fluorine substitution can always increase the lipophilicity of a molecule. Prediction of fluorine substitution and its effect on lipophilicity is not straightforward since it depends on the scaffold and proximal functionality. Monofluorination or trifluorination of saturated alkyl groups often decreases lipophilicity unlike in difluorination [14].

It is worth mentioning that the emergence of fluoroquinolones in the 1980s, brought fluorine to the forefront in medicinal chemistry. Fluoroquinolones are classified as second generation quinolones and have made a paradigm shift in scientific and clinical considerations, compounds such as norfloxacin, lomefloxacin, enoxacin, ofloxacin, and ciprofloxacin are good examples [15]. Notwithstanding, fluoroquinolones have a wide spectrum of antimicrobial activity. Ciprofloxacin (8) (Figure 5) is a stellar example of a fluoroquinolone to date with a broad spectrum of biological activities. The incorporation of fluorine at position-6 resulted in enhancing Gram-positive activities compared to other analogues. Fluorine plays a vital role in increasing the antibacterial potency [16], improving DNA gyrase complex binding and cell penetration.

2. Benzazoles

Benzo-fused heterocycles e.g., benzazoles, are known as privileged structures which have a wide range of biological activities and are very common as lead compounds and natural products (Figure 6).

The benzazole scaffold is widely distributed in nature, e.g., benzothiazole (9), benzimidazole (10), and benzooxazole (11) are considered essential core structures of many biomolecules such as in firefly luciferin (12), a benzothiazolyl derivative exhibiting bioluminescence [17] and a benzimidazole moiety exists as an axial ligand for cobalt in vitamin B12 (13) [18] (Figure 1).

Although benzazole is an aromatic system; however, its skeleton contains many active sites. These active sites provide several sites for further modifications and variance at positions-2, 4, 5, 6 or 7 and the most potently active benzazoles reported are those substituted at positions 2, 5, and 6 [19,20].
Benzimidazole is a popular nucleus in structural manipulation in medicinal chemistry and has been intensively discussed in the literature [19,21–24] and many benzimidazoles are reported to show anthelmintic [25,26], antimicrobial [27–32], anti-HIV [33–35], antiviral [36,37], anti-inflammatory [38,39], anticancer [40–44], anticonvulsant [45], antidiabetic [45,46], antihypertensive [47], anti-tuberculosis [48,49], antimalarial [50,51] and antioxidant [52,53] activities.

Moreover, the benzothiazole core is a widespread scaffold that has been extensively studied [54–59] and many derivatives are found to be antimicrobial [49,60–74], anticancer [75–91], anti-Alzheimer’s [92,93], anti-inflammatory [94–96], anti-HIV [97–99] anticonvulsant [100–102], antioxidant [39,103], anti-tuberculosis [104,105], antidiabetic [106,107], antidepressant [108], antihypertension [109,110] and antimalarial [111] agents.

In addition, benzoxazole derivatives possess a variety of biological activities such as antitumor [112–115], antituberculosis [116], antifungal [117], antimicrobial [118–123], antihypertension [124], antiviral [97,125], antihormonal [126], and radioligand agents [127–129]. Because of the aforementioned properties of both fluorine and benzazoles, efforts have been done by Nosova et al. to summarize several methods of synthesizing fluorinated benzazoles [130]. In the next sections, each type of benzoxazole incorporated with fluorine will be discussed expressing fluorine substitution effect on its biological activity.

2.1. Benzothiazoles Containing Fluorine

Fluorine stands out as a distinguishable moiety in medicinal chemistry and it has been incorporated in many heterocycles, e.g., benzothiazole to improve, enhance or get new biological activity. Benzothiazole containing fluorine draws a remarkable attention in drug design since benzothiazole is considered a privileged structure and its synthesis has been discussed in many literatures. Herein are several selected examples of benzothiazole analogues (Figure 7) that manifest the importance of merging fluorine on their biological activities.

Fluorine increases the cytotoxic activity which was supported by several studies. For example, Li et al. prepared a new series of antitumor agents by the combination of different pharmacophores of 2-substituted-3-sulfonyl aminobenzamide with benzothiazole, orthiazolo[5,4-b]pyridine, or [1,2,4]triazolo-[1,5-a]pyridine in an attempt to enhance the potency. As a result, nineteen structures were prepared, characterized and evaluated via MTT assay against four human cancer cell lines including HCT-116, A549, MCF-7 and U-87 MG. Among the prepared compounds, fluorinated compound 14 displays potent activities against the four cancer cell lines and its anticancer effect was further tested in the nude mouse HCT-116 colon adenocarcinoma xenograft model in which BEZ235 (30 mg/kg) was used as positive drug. From the experiment, they noticed a weight loss of tested animal while using BEZ235, unlike in compound 14 and that can be referred to its low toxicity [77].
In addition, Gill et al. developed a new series of N-alkylbromo-benzothiazoles with improved efficacy and selective action. Their findings [131] suggest that the benzothiazole bearing a strong electron-withdrawing atom such as fluorine at position-6, improves the cytotoxicity against particular cancer cell lines. Fluorine benzothiazole 15 exhibits the highest potency against leukemia THP-1 cancer cell line (IC$_{50}$ = 1 and 0.9 µM) and was higher than that of mitomycin-C (IC$_{50}$ = 1.5 µM) when compared to other non-fluorinated derivatives. Thus, this compound can be studied further to serve as a lead compound for anticancer drug development.

In another QSAR study undertaken by Kumbhare et al., a novel class of isoxazoles and triazoles linked 2-phenyl benzothiazoles were synthesized and tested against three cancer cell lines for their anticancer activity. As a result of this study, the introduction of fluorine, in the form of (–CF$_3$) group, enhanced the benzothiazole derivative 16 cytotoxicity against Colo-205 and A549 cells by causing an increase in the active caspase-3 and PARP and degradation of procaspase-8 and 9 proteins [132].
A novel series of aminobenzothiazole linked to pyrazolo[1,5-a]pyrimidine conjugates was synthesized by Kamal et al. and evaluated for their antitumor activities against five human cancer cell lines. The in vitro screening results disclosed that the 4-fluoro substituted derivatives exhibit a potent and selective anticancer activity with IC$_{50}$ value of 1.94–3.46 µM [133]. It has been subjected to more detailed biological studies such as cell cycle analysis, tubulin polymerization studies, and Immunohistochemistry studies on tubulin. Out of these studies, compound 17 showed G2/M cell cycle arrest and 65.9% inhibition of tubulin assembly in MCF-7 cells, which makes it a promising candidate for development of breast cancer therapy.

Noteworthy, Singh et al.’s finding [62] supported the notion that the presence of electron-withdrawing groups such as fluorine, chlorine, or a combination of both, significantly affects the antibacterial activity. The systematic SAR done by the same research group showed that fluorinated variant 18 containing two di-fluoro substituents offers the highest antibacterial activity against the six tested bacterial strains (both Gram-positive and gram-negative strains) except S. boydii strains. Moreover, the modification of substituents in the benzene ring also plays a vital role in their activity showing that the position of substituents at the benzene ring is critical in governing the antibacterial activity and fluorine has a potent effect in comparison to chlorine. For instance, placing fluoro group at positions-2 and 4 in the benzene ring enhance the potency unlike position-3 where activity is lost.

Spadaro et al. synthesized a series of benzothiazole derivatives targeting inhibition of 17β-HSD1 which is a novel target for estrogen-dependent diseases [134]. As they introduced different substituents with different electronic, lipophilic, steric, and H-bonding properties, they came out with two new lead compounds. The one in the amide series 19 shows that the difluoro-derivative in the benzoyl moiety increases the inhibitory activity of the compound to reach (IC$_{50}$ < 5 nM). This can be explained due to many factors; first, the favorable electronic effects applied by the fluorine on the H-bonding property of the OH, second, to the increased lipophilicity, or to the change in π-interacting properties of the aromatic ring.

Feng et al. prepared six cyanine dye substituted benzoxazolyl or benzothiazolyl groups and investigated them for their in vitro antiprotozoal activities. The in vitro tests were done using *P. falciparum* (K1), *Trypanosoma cruzi*, *T. brucei rhodesiense*, and *L. donovani* and the cytotoxicity of the compounds was evaluated using rat skeletal myoblasts (L-6 cells). The high antimalarial activity of the four fluorinated benzothiazolyl trimethine cyanines 20, 21, 22, 23 was attributed directly to the presence of the fluorine atom [135]. Compound 20 had a high activity against *T. cruzi*, IC$_{50}$ of 0.008 µM and a selectivity index of 193.7 and is used for Chagas disease treatment.

As mentioned previously, fluorine is a popular element which has been used as a labeling agent in the Positron Emission Tomography (PET) field [136]. Fluorine-18 labeled analogues are known as PET radio-ligands to detect and quantify the amyloid deposit distribution in human brains which is used for the detection of the development of Alzheimer’s Disease. Neumaier et al. reported the synthesis of three different [18F] fluoroethoxy-substituted benzothiazole derivatives. Among several PET markers prepared, [18F]$_2$-[4′-(methylamino)phenyl]-6-fluoroethoxybenzothiazole, (24) appeared as an appropriate amyloid imaging agent in terms of biokinetics and binding affinity for amyloid plaques. Its lipophilicity, ($log P_{oct}$) was 2.4 which agrees with the requirements for amyloid imaging agents such as PIB, SB13 and FDDNP so it can penetrate the blood brain barrier [137]. The in vitro binding affinity of 24 exhibits Ki = 7.2 nM, which falls within the expected range for specific Aβ binding.

A new series of benzothiazole Schiff base derivatives was prepared by Al-Harthy et al. These derivatives were synthesized based on the most potent antibiotic fluoroquinolone, ciprofloxacin, aiming to mimic its biological activity by bearing both fluorine and piperazine moieties. The fluoroquinolone directly inhibits bacterial DNA synthesis, resulting in cell death. The fluoroquinolone mechanism of action is believed to involve inhibition of DNA gyrase and topoisomerase IV enzymes, required for supercoiling replication and separation of bacterial DNA [138]. Fluorine plays a role in controlling DNA gyrase and bacterial potency. Amongst all, the derivative that
contains fluorine (25) shows a selective antitumor activity against DMS-53 human lung cancer cell line in comparison to primary HLMVECs [139].

Another manuscript was published later by the same researchers based on the above mentioned principle and it was based on a novel series of 5-fluoro-6-(4-methylpiperazin-1-yl)-substitutedphenylbenzo[d]thiazoles. The novel class was reported and screened against different bacteria and fungi strains. The molecule bearing electron withdrawing moiety by induction e.g., fluor in compound 26 has a role in enhancing antibacterial activity in comparison to the non-fluorinated derivatives [140].

2.2. Benzimidazoles Containing Fluorine

Similar to benzothiazole, benzimidazole is known as a privileged structure involved in many therapeutic agents and its derivatives were extensively mentioned in literature especially those with a fluorine moiety. Hereinafter, are some examples of benzimidazoles (Figure 8) containing fluorine to highlight its influence on their biological activities.

![Benzimidazole derivatives incorporating fluorine.](image-url)
To start with, Tonelli et al. prepared a set of benzimidazole derivatives as part of their continuous work in the chemistry and biological properties of benzimidazoles. In this study, a variety of moieties have been substituted at position-1 and 2 of benzimidazole; unsubstituted, basic, non-basic, aromatic, non-aromatic substitutions were synthetically introduced [37]. In order to highlight the importance of the presence of fluorine moiety, the derivative of benzimidazole with trifluromethyl at position-2, compound 27 exhibited higher potency against CVB-5, RSV and YFV, with EC50 of 11, 22, and 33 µM respectively compared to its analogue 28 having a 2-methyl moiety with EC50 of 47, >100, and 33 µM respectively. The importance of trifluoromethyl has been proven by the narrower spectrum of activity and lower potency compared to the 2-methyl benzimidazole analogue 28.

Zhang et al. synthesized a novel series of benzimidazole tertiary amine type of fluconazole analogues of potential antifungal activity. Fluconazole is an antifungal medicine used to treat infections caused by Candida albicans and Cryptococcus neoformans. The benzimidazole scaffold has been decorated with several moieties in order to achieve the optimal activity. For the purpose of improving the pharmacological properties, the phenyl has been substituted with chloro, fluoro, trifluromethyl, methyl and nitro moieties into target compounds which are believed to enhance the rate of absorption and in vivo drug transportation. It is worth noting that halo-benzimidazole possesses better activity in strain growth inhibition compared to alkyl benzimidazole. Compound 29 containing a 2,4-fluorinated benzyl ring shows the highest antifungal activity against C. albicans, S. cerevisiae and A. flavus fungi with MIC = 16–32 mg/mL [28].

Notably, a new series of benzimidazole analogues was designed by Reddy et al. by combining benzimidazole with other heterocycles such as pyrazole in what is called hybrid molecules whereby this hybridization is believed to improve the biological activity of molecules. The newly synthesized compounds were evaluated against three human tumor cell lines: lung (A549), breast (MCF-7), cervical (HeLa) and against normal keratinocyte (HaCaT) cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) growth inhibition assay. Structure activity relationship (SAR) studies of these hybrids concluded that the compounds with mono-substituted halogen (fluorine, chlorine, and bromine) on benzimidazole e.g., compound 30 with a fluorine appendage showed potent cytotoxicity against tested cancer cell lines [141]. On the other hand, the incorporation of trifluoromethyl (CF3) substitution at position-6 of benzimidazole resulted in moderate to lower cytotoxic activity.

It is worthy to note that designing molecules targeting the inhibition of tubulin polymerization is a highly attractive approach in designing anticancer candidates. Kamal et al. synthesized benzimidazole-oxindole conjugates and evaluated them against human breast cancer cell line (MCF-7) by inhibiting tubulin polymerization. The conjugates with mono fluoro, difluo, or trifluoromethyl moieties show a considerable antiproliferative activities. Their finding implies that conjugate 31 with a difluoro moiety at position 3 and 5 on phenyl ring showed a significant cytotoxicity against breast cancer cell line (MCF-7) with an IC50 value of 1.59 μM. Molecular docking studies have been performed to investigate the action mode of this compound and it indicated efficient binding with the colchicine binding site [133].

Zawawi et al. explored β-glucuronidase inhibitors using structure based design of benzimidazole with 2,5-disubstituted-1,3,4-oxadiazoles. The investigation revealed that the aromatic side chains directly attached to the oxadiazole moiety influence the inhibitory potential of the benzimidazole derivatives. The structure activity relationship (SAR) study proposed the reliance of inhibition upon the aromatic ring residue and its derivatives. For instance, fluoro groups in compounds (32, ortho-fluoro: IC50 = 19.16 ± 0.62 μM), 33; para-fluoro: IC50 = 13.14 ± 0.76 μM, 34; meta-fluoro: IC50 = 16.12 ± 0.36 μM) displayed excellent inhibition regardless of the position of fluorine at the aromatic ring [142].

Singh et al. research team’s interest is focused on the preparation of several di and tri substituted bis-benzimidazoles which incorporate electron donating (OCH3) and electron withdrawing groups (F, Cl) on the phenyl ring and test their ability to induce DNA cleavage in the presence of mammalian topoisomerase I. Hoechst 33342 and Hoechst 33258 are examples of bis-benzimidazole derivatives which have strong binding affinity to DNA causing catalytic activity inhibition of many enzymes.
involved in DNA replication and synthesis. It is worth to notice that the first derivatives of Hoechst having di-substituted groups, having halogen atoms as substituents, at 2-position of benzimidazole were synthesized by his team. A considerable change in absorbance was noticed with a significant hyperchromicity and a red shift was observed in the binding ability of compound 35 to CT-DNA. This observation was correlated to the presence of fluorine at the phenyl ring in the compound [27]. The small size of fluorine enables it to slip between the DNA base pairs and chelate with them leading to unwinding of the DNA strands resulting in the UV absorption hyperchromicity shift.

The cytotoxicity of the targeted bis-benzimidazoles were investigated against human tumor cell lines, which are cervix carcinoma cell line (HeLa), breast carcinoma cell line (MCF7) and brain glioma cell line (U87) in comparison to Hoechst and Camptothecin as a reference compound. The study showed remarkable cytotoxicity to human cancer cell lines, IC50 values of 5.5 µM against MCF7 and (IC50; 1.5 µM) in HeLa. Upon investigation of the inhibitory activity against purified human topoisomerase I, the bis-benzimidazoles exhibited effective enzyme inhibition even at low concentration of 25 µM.

El-Abadelah et al. reported a synthesis of a set of 2-arylbenzimidazoles 36 bearing both piperazine and fluorine. Their synthesis was based on mimicking the value of incorporating both fluorine and piperazine in ciprofloxacin in order to achieve a broad antimicrobial activity. The in vitro evaluation against E. coli, S. aureus, A. parasiticus and C. albicans showed no significant antibacterial activity at concentrations ≤100 µM [143].

In continuation of the abovementioned work, in 2005 Abdel-Jalil et al. replaced the aryl at 2-position with an aromatic ferrocenyl unit which was then converted into the hydrochloride salt to be tested against four different pathogenic Candida species. At least two derivatives showed interesting potency in comparison to that of azole-based (miconazole and ketoconazole) antifungal agents [144]. Another study on this area done by Abu-Elteen et al. who correlated the structures of the aforementioned 2-ferrocenyl-benzimidazoles with antifungal activity. The screening results showed that the three variants of compound 37 are the most potent against C. albicans [145].

2.3. Benzoxazoles Containing Fluorine

Benzoxazole is the third skeleton of benzazoles that exhibits a remarkable biological profile. Several benzoxazole derivatives discussed in the literature possess a wide range of biological activates mentioned earlier. In the next paragraph several examples explore the fluorine influence in some benzoxazole scaffolds (Figure 9).

Aiello et al. prepared a new class of fluorinated 2-aryl benzoxazoles, benzothiazoles and chromen-4-ones and evaluated their activity against MCF-7 and MDA 468 breast cancer cell lines and compared its activity to the known antitumor benzothiazole 38 [114]. Compound 38 is well known as a potent (GI50 < 0.1 nM) and selective in vitro antitumor agent in human cancer cell lines. The SAR study of these compounds shows that the presence of fluorine moiety is essential for the growth-inhibitory activity since the elimination of it or replacement of it with other halogens diminishes the inhibition ability. Although some benzoxazole derivatives 39, 40 showed excellent potency, theirs is lower than the antitumor potency of 38.

Jauhari et al. introduced a new class of 2-[[arylidene]cyanomethyl]-5-halobenzoxazoles as part of their ongoing work in preparing antitumor, antiviral, and antimicrobial candidates. The anticancer activity was done against four sets of human cell lines (HEPG-2, HeLa, WiDr, MCF-7) [146]. Interestingly, compound 41 with fluorine at position-5 exhibited a significant activity against all four tested cell lines and an exceptional antifungal activity against both A. flavus and A. niger. In antibacterial evaluation against Pseudomonas aeruginosa, Staphylococcus aureus, and Klebsiella pneumoniae, this new class showed a remarkable activity compared to other analogues.
In their effort to obtain orally potent VLA-4 inhibitors, Setoguchi et al. disclosed the optimum replacement lipophilic moiety which is 7-fluoro-2-(1-methyl-1H-indol-3-yl)-1,3-benzoxazolyl group (42) with (N'-phenylureido) phenyl group. The fluorine placed at position-7 in the benzoxazole skeleton provides a potent activity with IC$_{50}$ 4.7 and 156 nM (+3% HSA). The alteration of placing fluorine in the lipophilic moiety, made the compound easier to use with a certain serum protein as carrier, thus resulting in a high serum concentration. It also has excellent efficacy in a bronchial inflammatory model and favorable PK profile [147].

Omori et al. reported a novel benzoxazole NPY Y5 antagonist to construct an SAR study to identify a hit for a lead compound suitable for in vivo study [148]. From this SAR study, the replacement of ortho trifluoromethyl (compound 43) caused a decrease in the IC$_{50}$ compared with the meta & para position-substituted compounds 44, 45, respectively and on the other hand the alkoxy substituent at the para position (compound 46) has improved the potency.

3. Conclusions

Fluorine is a very important moiety in bioactive molecules whereby a single modification can lead to a tremendous increase in biological activities. Therefore, there is an escalating interest in introducing fluorine in designing and developing bioactive molecules. This review highlighted the influence of introducing fluorine in some benzazole scaffolds on the pharmacological and biological profiles of these systems. On the basis of various literature surveys, fluorine-containing benzazoles show improved biological activities. In most of the cases discussed in this review, the enhancement in biological activity and lowering of toxicity have been correlated to the introduction of the fluorine substituent on benzazoles.

Funding: This research was funded by His Majesty Trust Fund, grant number SR/SCI/CHM/19/01.

Acknowledgments: The authors would like to thank Wolfgang Voelter—University of Tübingen in Germany.

Conflicts of Interest: The authors declare no conflict of interest.
References

1. Pozharskii, A.F.; Soldatenkov, A.T.; Katritzky, A.R. Heterocycles and Health. In Heterocycles in Life and Society; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2011; pp. 139–183.

2. Pozharskii, A.F.; Soldatenkov, A.T.; Katritzky, A.R. Heterocycles in Agriculture. In Heterocycles in Life and Society; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2011; pp. 185–207.

3. Pozharskii, A.F.; Soldatenkov, A.T.; Katritzky, A.R. Heterocycles in Industry and Technology. In Heterocycles in Life and Society; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2011; pp. 209–246.

4. Wang, J.; Sánchez-Roselló, M.; Aceña, J.L.; del Pozo, C.; Sorochinsky, A.E.; Fustero, S.; Soloshonok, V.A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). Chem. Rev. 2014, 114, 2432–2506. [CrossRef] [PubMed]

5. Nenajdenko, V. Fluorine in Heterocyclic Chemistry Volume 1 5-Membered Heterocycles and Macrocycles; Nenajdenko, V., Ed.; Springer International Publishing: Cham, Switzerland, 2014.

6. Fjelbye, K.; Marigo, M.; Clausen, R.P.; Jørgensen, E.B.; Christoffersen, C.T.; Juhl, K. Elucidation of fluorine’s impact on pKa and in vitro Pgp-mediated efflux for a series of PDE9 inhibitors. MedChemComm 2018, 9, 893–896. [CrossRef] [PubMed]

7. Lou, Y.; Sweeney, Z.K.; Kuglstatter, A.; Davis, D.; Goldstein, D.M.; Han, X.; Hong, J.; Kocer, B.; Kondru, R.K.; Litman, R.; et al. Finding the perfect spot for fluorine: Improving potency up to 40-fold during a rational fluorine scan of a Bruton’s Tyrosine Kinase (BTK) inhibitor scaffold. Bioorg. Med. Chem. Lett. 2015, 25, 367–371. [CrossRef] [PubMed]

8. Olsen, J.; Seiler, P.; Wagner, B.; Fischer, H.; Tschopp, T.; Obst-Sander, U.; Banner, D.W.; Kansy, M.; Müller, K.; Diederich, F. A fluorine scan of the phenylamidinium needle of tricyclic thrombin inhibitors: Effects of fluorine substitution on pKa and binding affinity and evidence for intermolecular C–F···CN interactions. Org. Biomol. Chem. 2004, 2, 1339–1352. [CrossRef] [PubMed]

9. Cocker, M.S.; Spence, J.D.; Hammond, R.; deKemp, R.A.; Lum, C.; Wells, G.; Bernick, J.; Hill, A.; Nagpal, S.; Stotts, G.; et al. [18F]-Fluorodeoxyglucose PET/CT imaging as a marker of carotid plaque inflammation: Comparison to immunohistology and relationship to acuity of events. Int. J. Cardiol. 2018, 271, 378–386. [CrossRef]

10. Gu, S.C.; Ye, Q.; Yuan, C.X. Metabolic pattern analysis of 18F-FDG PET as a marker for Parkinson’s disease: A systematic review and meta-analysis. Rev. Neurosci. 2019, 3, 743–756. [CrossRef]

11. Vatsadze, S.Z.; Eremina, O.E.; Veselova, I.A.; Kalmykov, S.N.; Nenajdenko, V.G. 18F-Labelled catecholamine type radiopharmaceuticals in the diagnosis of neurodegenerative diseases and neuroendocrine tumours: Approaches to synthesis and development prospects. Rass. Chem. Rev. 2018, 87, 350–373. [CrossRef]

12. Ojima, I. Strategic Incorporation of Fluorine into Taxoid Anticancer Agents for Medicinal Chemistry and Biological Studies. J. Fluor. Chem. 2017, 198, 10–23. [CrossRef]

13. Wán, Z.-K.; Chenail, E.; Xiang, J.; Li, H.-Q.; Ipek, M.; Bard, J.; Hagen, S.; Heifetz, C.; Hutt, M.; Nichols, J.; Trehan, A. Quinoline Antibacterial Agents. Synthesis and Structure-Activity Relationships of 8-Substituted Quinoline-3-carboxylic Acids and 1,8-Naphthyridine-3-carboxylic Acids. J. Med. Chem. 1988, 31, 983–991. [CrossRef]

14. Smart, B.E. Fluorine substituent effects (on bioactivity). J. Fluor. Chem. 2001, 109, 3–11. [CrossRef]

15. Ball, P. Chapter 1—The Quinolones: History and Overview. In The Quinolones, 3rd ed.; Andriole, V.T., Ed.; Academic Press: San Diego, CA, USA, 2000; pp. 1–31.

16. Sanchez, J.; Domagala, J.; Hagen, S.; Heifetz, C.; Hutt, M.; Nichols, J.; Trehan, A. Quinoline Antibacterial Agents. Synthesis and Structure-Activity Relationships of 8-Substituted Quinoline-3-carboxylic Acids and 1,8-Naphthyridine-3-carboxylic Acids. J. Med. Chem. 1988, 31, 983–991. [CrossRef]

17. Joule, J.A.; Mills, K. Heterocyclic Nomenclature. In Heterocyclic Chemistry at a Glance; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2012; pp. 1–3.

18. Gilchrist, T.L. Heterocyclic Chemistry; John Wiley & Sons: New York, NY, USA, 1985.

19. Catalano, A.; Carocci, A.; Defrenza, I.; Muraglia, M.; Carrieri, A.; Van Bambeke, F.; Rosato, A.; Corbo, F.; Franchini, C. 2-Aminobenzothiazole derivatives: Search for new antifungal agents. Eur. J. Med. Chem. 2013, 64, 357–364. [CrossRef]
21. Gaba, M.; Singh, S.; Mohan, C. Benzimidazole: An emerging scaffold for analgesic and anti-inflammatory agents. *Eur. J. Med. Chem.* 2014, 76, 494–505. [CrossRef] [PubMed]

22. Błaszczak-Świątekiewicz, K.; Olszewska, P.; Mikiciuk-Olasik, E. Biological approach of anticancer activity of new benzimidazole derivatives. *Pharmocol. Rep.* 2014, 66, 100–106. [CrossRef]

23. Ajani, O.O.; Aderohunmu, D.V.; Ikpo, C.O.; Adedapo, A.E.; Olanrewaju, I.O. Functionalized Benzimidazole Scaffolds: Privileged Heterocycle for Drug Design in Therapeutic Medicine. *Arch. Pharm.* 2016, 349, 475–506. [CrossRef] [PubMed]

24. Bansal, Y.; Silakari, O. The therapeutic journey of benzimidazoles: A review. *Bioorg. Med. Chem.* 2012, 20, 6208–6236. [CrossRef]

25. Liu, G.-L.; Hu, Y.; Chen, X.-H.; Wang, G.-X.; Ling, F. Synthesis and anthelmintic activity of coumarin–imidazole hybrid derivatives against Dactylogyrus intermedius in goldfish. *Bioorg. Med. Chem. Lett.* 2016, 26, 5039–5043. [CrossRef]

26. Garg, K.; Bansal, Y.; Bansal, G.; Goel, R.K. Design, synthesis, and PASS-assisted evaluation of novel 2-substituted benzimidazole derivatives as potent anthelmintics. *Med. Chem. Res.* 2014, 23, 2690–2697. [CrossRef]

27. Singh, M.; Tandon, V. Synthesis and biological activity of novel inhibitors of topoisomerase I: 2-Aryl-substituted 2-bis-1H-benzimidazoles. *Eur. J. Med. Chem.* 2011, 46, 659–669. [CrossRef] [PubMed]

28. Zhang, H.-Z.; Damu, G.L.V.; Cai, G.-X.; Zhou, C.-H. Design, synthesis and antimicrobial evaluation of novel benzimidazole type of Fluconazole analogues and their synergistic effects with Chloromycin, Norfloxacin and Fluconazole. *Eur. J. Med. Chem.* 2013, 64, 329–344. [CrossRef] [PubMed]

29. Sharma, P.; Kumar, A.; Sharma, M.; Singh, J.; Bandyopadhyay, P.; Sathe, M.; Kaushik, M.P. Synthesis and exploration of QSAR model of 2-methyl-3-[2-(2-methylprop-1-en-1-yl)-1H-benzimidazol-1-yl]pyrimido [1,2-a]benzimidazol-4(3H)-one as potential antibacterial agents. *J. Enzym. Inhib. Med. Chem.* 2015, 41, 7695–7702. [CrossRef]

30. Desai, N.C.; Shihory, N.R.; Kotadiya, G.M.; Desai, P. Synthesis, antibacterial and antitubercular activities of benzimidazole bearing substituted 2-pyridone motifs. *Eur. J. Med. Chem.* 2014, 82, 480–489. [CrossRef] [PubMed]

31. Huigens, R.W.; Reyes, S.; Reed, C.S.; Bunders, C.; Rogers, S.A.; Steinhauser, A.T.; Melander, C. The chemical synthesis and antibiotic activity of a diverse library of 2-aminobenzimidazole small molecules against MRSA and multidrug-resistant A. baumannii. *Bioorg. Med. Chem.* 2010, 18, 663–674. [CrossRef] [PubMed]

32. Jin, Q.; Li, F.; Li, Y.; Jin, F.; Jiang, L. Synthesis and antifungal activity of novel α-alkoxyimino-(1H-benzoimidazol-2-yl)acetonitriles containing piperazine moiety. *Res. Chem. Intermed.* 2015, 41, 7695–7702. [CrossRef]

33. Pan, T.; He, X.; Chen, B.; Chen, H.; Geng, G.; Luo, H.; Zhang, H.; Bai, C. Development of benzimidazole derivatives to inhibit HIV-1 replication through protecting APOBEC3G protein. *Eur. J. Med. Chem.* 2015, 95, 500–513. [CrossRef]

34. Miller, J.F.; Turner, E.M.; Gudmundsson, K.S.; Jenkinson, S.; Spaltenstein, A.; Thomson, M.; Wheelan, P. Novel N-substituted benzimidazole CXCR4 antagonists as potential anti-HIV agents. *Bioorg. Med. Chem. Lett.* 2010, 20, 2125–2128. [CrossRef]

35. Monforte, A.-M.; Ferro, S.; De Luca, L.; Lo Surdo, G.; Morreale, F.; Pannecoque, C.; Balzarini, J.; Chimirri, A. Design and synthesis of N1-aryl-benzimidazoles 2-substituted as novel HIV-1 non-nucleoside reverse transcriptase inhibitors. *Bioorg. Med. Chem.* 2014, 22, 1459–1467. [CrossRef]

36. Tonelli, M.; Simone, M.; Tasso, B.; Novelli, F.; Boido, V.; Sparatore, F.; Paglietti, G.; Pricl, S.; Giliberti, G.; Blois, S.; et al. Antiviral activity of benzimidazole derivatives. II. Antiviral activity of 2-phenylbenzimidazole derivatives. *Bioorg. Med. Chem.* 2010, 18, 2937–2953. [CrossRef]

37. Tonelli, M.; Novelli, F.; Tasso, B.; Vazza, I.; Sparatore, A.; Boido, V.; Sparatore, F.; La Colla, P.; Sanna, G.; Giliberti, G.; et al. Antiviral activity of benzimidazole derivatives. III. Novel anti-CVB-5, anti-RSV and anti-Sb-1 agents. *Bioorg. Med. Chem.* 2014, 22, 4893–4909. [CrossRef]

38. Chen, G.; Liu, Z.; Zhang, Y.; Shan, X.; Jiang, L.; Zhao, Y.; He, W.; Feng, Z.; Yang, S.; Liang, G. Synthesis and Anti-inflammatory Evaluation of Novel Benzimidazole and Imidazopyridine Derivatives. *ACS Med. Chem. Lett.* 2013, 4, 69–74. [CrossRef] [PubMed]
39. vanucci-bacqué, C.; Carayon, C.; Bernis, C.; Camare, C.; Negre-Salvayre, A.; Bedos-Belval, F.; Baltas, M. Synthesis, antioxidant and cytoprotective evaluation of potential antiatherogenic phenolic hydrazones. A structure–activity relationship insight. Bioorg. Med. Chem. 2014, 22, 4269–4276.

40. Yurttaş, L.; Demirayak, Ş.; Çiftçi, G.A.; Yıldırım, Ş.U.; Kaplançıkli, Z.A. Synthesis and Biological Evaluation of Some 1,2-Disubstituted Benzimidazole Derivatives as New Potential Anticancer Agents. Arch. Pharm. 2013, 346, 403–414. [CrossRef] [PubMed]

41. Refaat, H.M. Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives. Eur. J. Med. Chem. 2010, 45, 2949–2956. [CrossRef] [PubMed]

42. Alkahtani, A.Y.; Abbas, A.Y.; Wang, S. Synthesis and biological evaluation of benzo[d]imidazole derivatives as potential anti-cancer agents. Bioorg. Med. Chem. Lett. 2012, 22, 1317–1321. [CrossRef]

43. El-Nassan, H.B. Synthesis, antitumor activity and SAR study of novel [1,2,4]triazino[4,5-a]benzimidazole derivatives. Eur. J. Med. Chem. 2012, 53, 22–27. [CrossRef] [PubMed]

44. Welsh, A.; Rylands, L.-I.; Arion, V.B.; Prince, S.; Smith, G.S. Synthesis and antiproliferative activity of benzimidazole-based, trinuclear neutral cyclometallated and cationic, N,N-chelated ruthenium(ii) complexes. Dalton Trans. 2020, 49, 1143–1156. [CrossRef]

45. Shingalapur, R.V.; Hosamani, K.M.; Keri, R.S.; Hugar, M.H. Derivatives of benzimidazole pharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. Eur. J. Med. Chem. 2010, 45, 1753–1759. [CrossRef]

46. Hidalgo-Figueroa, S.; Navarrete-Vázquez, G.; Estrada-Soto, S.; Giles-Rivas, D.; Alarcon-Aguilar, F.J.; León-Rivera, I.; Giacoman-Martinez, A.; Miranda Pérez, E.; Almanza-Pérez, J.C. Discovery of new dual PPARy-GPR40 agonists with robust antidiabetic activity: Design, synthesis and in combo drug evaluation. Biomed. Pharmacother. 2017, 90, 53–61. [CrossRef]

47. Zhu, W.; Da, Y.; Wu, D.; Zheng, H.; Zhu, L.; Wang, L.; Yan, Y.; Chen, Z. Design, synthesis and biological evaluation of new 5-nitro benzimidazole derivatives as AT1 antagonists with anti-hypertension activities. Bioorg. Med. Chem. 2014, 22, 2294–2302. [CrossRef]

48. Kalalbandi, V.K.A.; Seetharamappa, J.; Katrahalli, U.; Bhat, K.G. Synthesis, crystal studies, anti-tuberculosis and cytotoxic studies of 1-[2E]-3-phenylprop-2-enoyl]-1H-benzimidazole derivatives. Eur. J. Med. Chem. 2014, 79, 194–202. [CrossRef] [PubMed]

49. Patel, R.V.; Patel, P.K.; Kumari, P.; Rajani, D.P.; Chikhalia, K.H. Synthesis of benzimidazolyl-1,3,4-oxadiazol-2-ythio-N-phenyl (benzothiazolyl) acetamides as antibacterial, antifungal and antituberculosis agents. Eur. J. Med. Chem. 2012, 53, 41–51. [CrossRef] [PubMed]

50. Mayence, A.; Vanden Eynde, J.J.; Kaiser, M.; Brun, R.; Yarlett, N.; Huang, T.L. Bis(oxyphenylene) benzimidazoles: A novel class of anti-Plasmodium falciparum agents. Bioorg. Med. Chem. 2011, 19, 7493–7500. [CrossRef] [PubMed]

51. Roman, G.; Crandall, I.E.; Szarek, W.A. Synthesis and anti-Plasmodium activity of benzimidazole analogues structurally related to astemizole. ChemMedChem 2013, 8, 1795–1804. [CrossRef]

52. Neochoritis, C.G.; Zarganes-Tzitzikas, T.; Tsoleridis, C.A.; Stephanidou-Stephanatou, J.; Kontogiorgis, C.A.; Hadjipavlou-Litina, D.J.; Choli-Papadopoulou, T. One-pot microwave assisted synthesis under green bases and pyrimido[1,2-a]benzimidazol-3(4H)-ones. Eur. J. Med. Chem. 2011, 46, 297–306. [CrossRef]

53. Arora, R.K.; Kaur, N.; Bansal, Y.; Bansal, G. Novel coumarin–benzimidazole derivatives as antioxidants and safer anti-inflammatory agents. Acta Pharm. Sin. B 2014, 4, 368–375. [CrossRef]

54. Keri, R.S.; Patil, M.R.; Patil, S.A.; Budagumpi, S. A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry. Eur. J. Med. Chem. 2015, 89, 207–251. [CrossRef]

55. Rouf, A.; Tanyeli, C. Bioactive thiazole and benzothiazole derivatives. Eur. J. Med. Chem. 2015, 97, 911–927. [CrossRef]

56. Sharma, P.C.; Sinhmar, A.; Sharma, A.; Rajak, H.; Pathak, D.P. Medicinal significance of benzothiazole scaffold: An insight view. J. Enzym. Inhib. Med. Chem. 2013, 28, 240–266. [CrossRef]

57. Gill, R.K.; Rawal, R.K.; Barirwal, J. Recent Advances in the Chemistry and Biology of Benzothiazoles. Arch. Pharm. 2015, 348, 155–178. [CrossRef]

58. Ahmed, K.; Yellamelli Valli Venkata, S.; Mohammed, N.A.K.; Sultana, F.; Methuku, K.R. Recent advances on structural modifications of benzothiazoles and their conjugate systems as potential chemotherapeutics. Expert Opin. Investig. 2012, 21, 619–635. [CrossRef] [PubMed]
59. Kamal, A.; Syed, M.A.H.; Mohammed, S.M. Therapeutic potential of benzothiazoles: A patent review (2010–2014). Expert Opin. Ther. Pat. 2015, 25, 335–349. [CrossRef]

60. Defrenza, I.; Catalano, A.; Carocci, A.; Carriani, A.; Muraglia, M.; Rosato, A.; Corbo, F.; Franchini, C. 1,3-Benzothiazoles as Antimicrobial Agents. J. Heterocycl. Chem. 2015, 52, 1705–1712. [CrossRef]

61. Kaplan-Ozen, C.; Tekiner-Gulbas, B.; Foto, E.; Yildiz, I.; Diril, N.; Aki, E.; Yalcin, I. Benzothiazole derivatives as human DNA topoisomerase IIa inhibitors. Med. Chem. Res. 2013, 22, 5798–5808. [CrossRef]

62. Singh, M.; Tilak, R.; Nath, G.; Awasthi, S.; Agarwal, A. Design, synthesis and antimicrobial activity of novel benzothiazole analogs. Eur. J. Med. Chem. 2013, 63, 635–644. [CrossRef]

64. Bhagat, T.M.; Deshmukh, S.K.; Kuberkar, S.V. Novel Synthesis and Antimicrobial Activity of 3-Substituted 5-bromo-7-methyl-1,2,4-triazolo-[3,4-b]-benzothiazoles. J. Heterocycl. Chem. 2012, 49, 873–876. [CrossRef]

65. Badne, S.G.; Swamy, D.K.; Bhosale, V.N.; Kuberkar, S.V. Novel synthesis and biological activity of 2-substituted derivatives of 3-cyano-4-imino-2-methylthio-8-methoxy-4H-pyrimido[2,1-b][1,3]benzothiazole and 3-amino-4-imino-8-methoxy-2H-pyrazolo[3′,4′:4,5]pyrimido[2,1-b][1,3]benzothiazole. J. Heterocycl. Chem. 2011, 48, 849–855. [CrossRef]

66. Ouyang, L.; Huang, Y.; Zhao, Y.; He, G.; Xie, Y.; Liu, J.; He, J.; Liu, B.; Wei, Y. Preparation, antibacterial evaluation and preliminary structure–activity relationship (SAR) study of benzothiazol- and benzoxazol-2-amine derivatives. Bioorg. Med. Chem. Lett. 2012, 22, 3044–3049. [CrossRef] [PubMed]

67. Kumbhare, R.; Dadmal, T.; Pamanji, R.; Kosurkar, U.; Velatooru, L.; Appalanaidu, K.; Rao, K.; Rao, V. Synthesis of novel fluoro 1,2,3-triazole tagged amino bis(benzothiazole) derivatives, their antimicrobial and anticaner activity. Med. Chem. Res. 2014, 23, 4404–4413. [CrossRef] [PubMed]

68. Shaikh, F.; Patel, N.; Sanna, G.; Busonera, B.; LaColla, P.; Rajani, D. Synthesis of some new 2-amino-6-thiocyanato benzothiazole derivatives bearing 2,4-thiazolidinediones and screening of their in vitro antimicrobial, antitubercular and antiviral activities. Med. Chem. Res. 2015, 24, 3129–3142. [CrossRef]

69. Seenaiah, D.; Reddy, P.; Reddy, G.; Padmaja, A.; Padmavathi, V.; Krishna, N. Synthesis, antimicrobial and cytotoxic activities of pyrimidinyl benzoxazole, benzothiazole and benzimidazole. Eur. J. Med. Chem. 2014, 77, 1–7. [CrossRef] [PubMed]

70. Malik, J.K.; Soni, H.; Singhai, A.K. Synthesis, characterization and evaluation for antifungal activity of substituted diaryl imidazo [2,1-b]-benzothiazole. J. Pharm. Res. 2013, 7, 39–46. [CrossRef]

71. Xie, X.; Yana, Y.; Zhu, N.; Liu, G. Benzothiazoles exhibit broad-spectrum antitumor activity: Their potency, structureactivity and structuremetabolism relationships. Eur. J. Med. Chem. 2014, 76, 67–78. [CrossRef]

72. Noolvi, M.N.; Patel, H.M.; Kaur, M. Benzothiazoles: Search for anticancer agents. Eur. J. Med. Chem. 2012, 54, 447–462. [CrossRef]

73. Li, H.; Wang, X.-M.; Wang, J.; Shao, T.; Li, Y.P.; Mei, Q.-B.; Lu, S.-M.; Zhang, S.-Q. Combination of 2-methoxy-3-phenylsulfonamidobenzamide and 2-aminobenzothiazole to discover novel anticancer agents. Bioorg. Med. Chem. 2014, 22, 3739–3748. [CrossRef]
78. Gurdal, E.E.; Durmaz, I.; Cetin-Atalay, R.; Yarim, M. Cytotoxic activities of some benzothiazole-piperazine derivatives. *J. Enzym. Inhib. Med. Chem.* 2015, 30, 649–654. [CrossRef] [PubMed]

79. Ma, J.; Chen, D.; Lu, K.; Wang, L.; Han, X.; Zhao, Y.; Gong, P. Design, synthesis, and structure–activity relationships of novel benzothiazole derivatives bearing the ortho-hydroxy N-carbamoylahydrazone moiety as potent antitumor agents. *Eur. J. Med. Chem.* 2014, 86, 257–269. [CrossRef] [PubMed]

80. Ma, J.; Bao, G.; Wang, L.; Li, W.; Xu, B.; Du, B.; Lv, J.; Zhai, X.; Gong, P. Design, synthesis, biological evaluation and preliminary mechanism study of novel benzothiazole derivatives bearing indole-based moieties as potent antitumor agents. *Eur. J. Med. Chem.* 2015, 96, 173–186. [CrossRef] [PubMed]

81. Hong, S.; Kim, J.; Yun, S.-M.; Lee, H.; Park, Y.; Hong, S.-S.; Hong, S. Discovery of New Benzothiazole-Based Inhibitors of Breakpoint Cluster Region-Abelson Kinase Including the T315I Mutant. *J. Med. Chem.* 2013, 56, 3531–3545. [CrossRef]

82. Okaniwa, M.; Hirose, M.; Arita, T.; Yabuki, M.; Nakamura, A.; Takagi, T.; Kawamoto, T.; Uchiyama, N.; Sumita, A.; Tsutsumi, S.; et al. Discovery of a Selective Kinase Inhibitor (TAK-632) Targeting Pan-RAF Inhibition: Design, Synthesis, and Biological Evaluation of C-7-Substituted 1,3-Benzothiazole Derivatives. *J. Med. Chem.* 2013, 56, 6478–6494. [CrossRef]

83. Gurdal, E.E.; Buclulgan, E.; Durmaz, I.; Cetin-Atalay, R.; Yarim, M. Synthesis and anticancer activity evaluation of some benzothiazole-piperazine derivatives. *Anticancer Agents Med. Chem.* 2015, 15, 382–389. [CrossRef]

84. Xie, X.; Li, H.; Wang, J.; Mao, S.; Xin, M.; Lu, S.; Mei, Q.; Zhang, S. Synthesis and anticancer effects evaluation of 1-alkyl-3-(6-(2-methoxy-3-sulfonylaminopyridin-5-yl)benzo[d]thiazol-2-yl)urea as anticancer agents with low toxicity. *Bioorg. Med. Chem.* 2015, 23, 6477–6485. [CrossRef]

85. Wang, Z.; Shi, X.-H.; Wang, J.; Zhou, T.; Xu, Y.-Z.; Huang, T.-T.; Li, Y.-F.; Zhao, Y.-L.; Yang, L.; Yang, S.-Y.; et al. Synthesis, structure–activity relationships and preliminary antitumor evaluation of benzothiazole-2-thiol derivatives as novel apoptosis inducers. *Bioorg. Med. Chem. Lett.* 2011, 21, 1097–1101. [CrossRef]

86. Kamal, A.; Tamboli, J.R.; Nayak, V.L.; Adil, S.F.; Vishnuvardhan, M.V.P.S.; Ramakrishna, S. Synthesis of pyrazolo[1,5-a]pyrimidine linked aminobenzothiazole conjugates as potential anticancer agents. *Bioorg. Med. Chem.* 2015, 23, 3208–3215. [CrossRef]

87. Murty, M.S.R.; Rao, B.R.; Katiki, M.R.; Nath, L.R.; Anto, R.J. Synthesis of piperazinyl benzothiazole/benzoazazole derivatives coupled with 1,3,4-oxadiazole-2-thiol: Novel hybrid heterocycles as anticancer agents. *Med. Chem. Res.* 2013, 22, 4980–4991. [CrossRef]

88. Nagarapu, L.; Vanaparthi, S.; Bantu, R.; Ganesh Kumar, C. Synthesis of novel benzo[4,5]thiazolo[1,2-a]pyrimidine-3-carboxylate derivatives and biological evaluation as potential anticancer agents. *Eur. J. Med. Chem.* 2013, 69, 817–822. [CrossRef]

89. Gabr, M.T.; El-Gohary, N.S.; El-Bendary, E.R.; El-Kerdawy, M.M. Synthesis and in vitro antitumor activity of new series of benzothiazole and pyrimido[2,1-b]benzothiazole derivatives. *Eur. J. Med. Chem.* 2014, 85, 576–592. [CrossRef] [PubMed]

90. Kumbhare, R.M.; Dadmal, T.; Kosurkar, U.; Sridhar, V.; Rao, J.V. Synthesis and cytotoxic evaluation of thiourea and N-bis-benzothiazole derivatives: A novel class of cytotoxic agents. *Bioorg. Med. Chem. Lett.* 2012, 22, 453–455. [CrossRef] [PubMed]

91. Xuan, W.; Ding, W.; Hui, H.-X.; Zhang, S.-Q. Synthesis and cytotoxic activity of diaryl urea derivatives with a 4-methylpiperazinylcarbonyl moiety. *Med. Chem. Res.* 2013, 22, 3857–3862. [CrossRef]

92. Geng, J.; Li, M.; Wu, L.; Ren, J.; Qu, X. Liberation of Copper from Amyloid Plaques: Making a Risk Factor Useful for Alzheimer’s Disease Treatment. *J. Med. Chem.* 2012, 55, 9146–9155. [CrossRef] [PubMed]

93. Valasani, K.R.; Hu, G.; Chaney, M.O.; Yan, S.S. Structure-Based Design and Synthesis of Benzothiazole Phosphonate Analogues with Inhibitors of Human ABAD-Aβ for Treatment of Alzheimer’s disease. *Chem. Biol. Drug Des.* 2013, 81, 238–249. [CrossRef]

94. Nalawade, S.; Deshmukh, V.; Chaudhari, S. Design, microwave assisted synthesis and pharmacological activities of substituted pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate derivatives. *J. Pharm. Res.* 2013, 7, 433–438. [CrossRef]

95. Abbas, E.M.H.; Amin, K.M.; El-Hamouly, W.S.; Dawood, D.H.; Abdalla, M.M. Synthesis, anti-inflammatory and antinociceptive activity of some novel benzothiazole derivatives. *Res. Chem. Intermed.* 2015, 41, 2537–2555. [CrossRef]
96. Kishore, P.; Kaur, R.; Chandrasekaran, B.; Bala, M.; Gill, D.; Rao, V.; Rao, R.; Mailavaram, R. Synthesis, anti-inflammatory evaluation, and docking studies of some new thiazole derivatives. *Med. Chem. Res.* **2014**, *23*, 2780–2792.

97. Jonckers, T.H.M.; Rouan, M.-C.; Haché, G.; Schepens, W.; Hallenberger, S.; Baumeister, J.; Sasaki, J.C. Benzoxazole and benzo[b]thiazole amides as novel pharmacokinetic enhancers of HIV protease inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4998–5002. [CrossRef]

98. Bhattarai, D.; Trivedi, J.; Parekh, S.; Savant, M.; Thakrar, S.; Bavishi, A.; Radadiya, A.; Vala, H.; Lunagariya, J.; Parmar, M.; et al. Synthesis and in vitro anti-HIV activity of N-1,3-benz[d]thiazol-2-yl-2-(2-oxo-2H-chromen-4-yl)acetamide derivatives using MTT method. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3433–3436. [CrossRef] [PubMed]

99. Pitta, E.; Geroniaki, A.; Surmava, S.; Eleftheriou, P.; Mehta, V.P.; Van der Eycken, E.V. Synthesis and HIV-1 RT inhibitory action of novel (4/6-substituted benz[d]thiazol-2-yl)-thiazolidin-4-ones. Divergence from the non-competitive inhibition mechanism. *J. Enzym. Inhib. Med. Chem.* **2013**, *28*, 113–122. [CrossRef] [PubMed]

100. Ali, R.; Siddiqui, N. New Benz[d]thiazol-2-yl-aminoacetamides as Potential Anticonvulsants: Synthesis, Activity and Prediction of Molecular Properties. *Arch. Pharm.* **2015**, *348*, 254–265. [CrossRef]

101. Navale, A.; Pawar, S.; Deodhar, M.; Kale, A. Synthesis of substituted benz[d]thiazol-2-yl-carbamates as potential anticonvulsants. *Med. Chem. Res.* **2013**, *22*, 4316–4321. [CrossRef]

102. Amnerkar, N.; Bhusari, K. Synthesis, anticonvulsant activity and 3D-QSAR study of some prop-2-eneamido and 1-acyethyl-pyrazolin derivatives of aminobenzothiazole. *Eur. J. Med. Chem.* **2010**, *45*, 149–159. [CrossRef]

103. Cressier, D.; Prouillac, C.; Hernandez, P.; Amourette, C.; Diserbo, M.; Lion, C.; Rima, G. Synthesis, antioxidant properties and radioprotective effects of new benzothiazoles and thiadiazoles. *Bioorg. Med. Chem.* **2009**, *17*, 5275–5284. [CrossRef]

104. Chikhale, R.; Menghani, S.; Babu, R.; Bansode, R.; Bhargavi, G.; Karodia, N.; Rajasekharan, V.; Paradkar, A.; Khedekar, V.N.; Bairwa, V.K.; Satardekar, K.; Bellubi, A. Novel 2-(4-aryloxybenzylidene)hydrazinyl]benzothiazole derivatives as anti-tubercular agents. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 649–652. [CrossRef]

105. Meltzer-Mats, E.; Babai-Shani, G.; Pasternak, L.; Uritsky, N.; Getter, T.; Viskind, O.; Eckel, J.; Cerasi, E.; Senderowitz, H.; Sasson, E.; et al. Synthesis and Mechanism of Hypoglycemic Activity of Benzothiazole Derivatives. *J. Med. Chem.* **2013**, *56*, 5335–5331. [CrossRef]

106. Patil, V.S.; Nandre, K.P.; Ghosh, S.; Rao, V.J.; Chopade, B.A.; Sridhar, B.; Bhosale, S.V.; Bhosale, S.V. Synthesis, crystal structure and antidiabetic activity of substituted (E)-3-(Benzo[d]thiazol-2-ylamino)phenylprop-2-en-1-one. *Eur. J. Med. Chem.* **2015**, *96*, 30–46. [CrossRef]

107. Wang, S.; Chen, Y.; Zhao, S.; Xu, X.; Liu, X.; Liu, B.-F.; Zhang, G. Synthesis and biological evaluation of a series of benzoxazole/benzothiazole-containing 2,3-dihydrobenzo[b][1,4]dioxine derivatives as potential antidepressants. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1766–1770. [CrossRef] [PubMed]

108. Kalavagunta, P.K.; Bagul, P.K.; Jallapally, A.; Kantevari, S.; Banerjee, S.K.; Ravirala, N. Design and green synthesis of 2-(diarylalkyl)aminobenzothiazole derivatives and their dual activities as angiotensin converting enzyme inhibitors and calcium channel blockers. *Eur. J. Med. Chem.* **2014**, *83*, 344–354. [CrossRef] [PubMed]

109. Deprez, P.; Temal, T.; Jary, H.; Auberval, M.; Lively, S.; Guédin, D.; Vevert, J.-P. New potent calcimimetics: II. Discovery of benzothiazole trisubstituted ureas. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2455–2459. [CrossRef]

110. Venugopala, K.N.; Krishnappa, M.; Nayak, S.K.; Subrahmanya, B.K.; Vadera, P.; Chalannavar, R.K.; Gleiser, R.M.; Odhav, B. Synthesis and antimosquito properties of 2,6-substituted benz[d]thiazole and 2,4-substituted benzo[d]thiazole analogues against Anopheles arabiensis. *Eur. J. Med. Chem.* **2013**, *65*, 295–303. [CrossRef] [PubMed]

111. Rida, S.M.; Ashour, F.A.; El-Hawash, S.A.M.; ElSemary, M.M.; Badr, M.H.; Shalaby, M.A. Synthesis of some novel benzoxazole derivatives as anticancer, anti-HIV-1 and antimicrobial agents. *Eur. J. Med. Chem.* **2005**, *40*, 949–959. [CrossRef]

112. Xiang, P.; Zhou, T.; Wang, L.; Sun, C.-Y.; Hu, J.; Zhao, Y.-L.; Yang, L. Novel Benzo[b]thiazole, Benzimidazole and Benzo[d]thiazole Derivatives as Potential Antitumor Agents: Synthesis and Preliminary in Vitro Biological Evaluation. *Molecules* **2012**, *17*, 873–883. [CrossRef]
114. Aiello, S.; Wells, G.; Stone, E.L.; Kadri, H.; Bazzi, R.; Bell, D.R.; Stevens, M.F.G.; Matthews, C.S.; Bradshaw, R.D.; Westwell, A.D. Synthesis and Biological Properties of Benzothiazole, Benzoxazole, and Chromen-4-one Analogues of the Potent Antitumor Agent 2-(3,4-Dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610, NSC 721648). J. Med. Chem. 2008, 51, 5135–5139. [CrossRef]

115. Omar, A.M.E.; AboulWafa, O.M.; El-Shoukrofy, M.S.; Amr, M.E. Benzoxazole derivatives as new generation of anti-breast cancer agents. Bioorg. Chem. 2020, 96, 21. [CrossRef]

116. Ramalingan, C.; Balasubramanian, S.; Kabilan, S.; Vasudevan, M. Synthesis and study of antibacterial and antifungal activities of novel 1-[2-(benzoxazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-ones. Eur. J. Med. Chem. 2004, 39, 527–533. [CrossRef] [PubMed]

117. Tekiner-Gulbas, B.; Temiz-Arpaci, O.; Yildiz, I.; Altanlar, N. Synthesis and in vitro antimicrobial activity of new 2-[p-substituted-benzyl]-5-[substituted-carbonylamino]benzoxazoles. J. Med. Chem. 2007, 42, 1293–1299. [CrossRef] [PubMed]

118. Ramalingan, C.; Balasubramanian, S.; Kabilan, S.; Vasudevan, M. Synthesis and study of antibacterial and antifungal activities of novel 1-[2-(benzoxazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-ones. Eur. J. Med. Chem. 2004, 39, 527–533. [CrossRef] [PubMed]

119. Tekiner-Gulfas, B.; Temiz-Arpaci, O.; Yildiz, I.; Altanlar, N. Synthesis and in vitro antimicrobial activity of new 2-[p-substituted-benzyl]-5-[substituted-carbonylamino]benzoxazoles. J. Med. Chem. 2007, 42, 1293–1299. [CrossRef] [PubMed]

120. Vinsova, J.; Cermakova, K.; Tomeckova, A.; Ceckova, M.; Jampilek, J.; Cermak, P.; Kunes, J.; Dolezale, M.; Staud, F. Synthesis and antimicrobial evaluation of new 2-substituted 5,7-di-tert-butylbenzoxazoles. Bioorg. Med. Chem. Lett. 2006, 14, 5850–5856. [CrossRef] [PubMed]

121. Vinsova, J.; Horak, V.; Buchta, V.; Kaustova, J. Highly Lipophilic Benzoxazoles with Potential Antibacterial Activity. Molecules 2005, 10, 783–793. [CrossRef] [PubMed]

122. Arisoy, M.; Ozlem, T.-A.; Fatma, K.-O.; Selda, O. Synthesis and antimicrobial activity of novel benzoxazoles. Z. Naturforsch. 2012, 67, 466–472. [CrossRef]

123. Murty, M.S.R.; Ram, K.R.; Rao, R.V.; Yadav, J.S.; Murty, U.S.N.; Kumar, K.P. CsF–Celite catalyzed facile N-alkylation of 2(3H)-benzoxazolones and antimicrobial properties of 2-substituted benzoxazole and 3-substituted(2-3H)-benzoxazolone derivatives. Med. Chem. Res. 2011, 20, 626–636. [CrossRef]

124. Sweis, R.F.; Hunt, J.A.; Kallashi, F.; Hammonda, M.L.; Chen, Y.; Eveland, S.S.; Guo, Q.; Hyland, S.A.; Milot, D.P.; Cumiskey, A.-M.; et al. 2-(4-Carbonylphenyl)benzoxazole inhibitors of CETP: Scaffold design and advancement in HDLc-raising efficacy. Bioorg. Med. Chem. Lett. 2011, 21, 1890–1895. [CrossRef]

125. Medebielle, M.; Ait-Mohand, S.; Burkhloder, C.; Dolbier, W.R., Jr.; Laumond, G.R.; Aubertin, A.-M. Syntheses of new difluoromethylene benzoxazole and 1,2,4-oxadiazole derivatives, as potent non-nucleoside HIV-1 reverse transcriptase inhibitors. J. Fluor. Chem. 2005, 126, 535–542. [CrossRef]

126. Jin, C.; Fix, S.E.; Keple, J.A.; Cook, C.E. Synthesis and antihormonal properties of novel 11b-benzoxazole-substituted steroids. Bioorg. Med. Chem. Lett. 2012, 22, 1705–1708. [CrossRef]

127. Alagille, D.; Baldwin, R.M.; Tamagnan, G.D. One-step synthesis of 2-arylbenzothiazole (‘BTA’) and -benzoxazole precursors for in vivo imaging of β-amyloid plaques. Tetrahedron Lett. 2005, 46, 1349–1351. [CrossRef]

128. Gao, M.; Wang, M.; Hutchins, A.D.; Zheng, Q.-H. Synthesis of new carbon-11 labeled benzoxazole derivatives for PET imaging of 5-HT3 receptor. Eur. J. Med. Chem. 2008, 43, 1570–1574. [CrossRef] [PubMed]

129. Wang, X.; Cui, M.; Yu, P.; Li, Z.; Yang, Y.; Jia, H.; Liu, B. Synthesis and biological evaluation of novel technetium-99m labeled phenylbenzoxazole derivatives as potential imaging probes for β-amyloid plaques in brain. Bioorg. Med. Chem. Lett. 2012, 22, 4327–4331. [CrossRef] [PubMed]

130. Nosova, E.V.; Mochul’skaya, N.N.; Kotovskaya, S.K.; Lipunova, G.N.; Charushin, V.N. Fluorinated benzazoles and benzazines. Heteroat. Chem. 2006, 17, 579–594. [CrossRef]

131. Gill, R.K.; Singh, G.; Sharma, A.; Bedi, P.M.S.; Saxena, A.K. Synthesis, cytotoxic evaluation, and in silico studies of substituted N-alkylbromo-benzothiazoles. Med. Chem. Res. 2013, 22, 4211–4222. [CrossRef]

132. Kumbhare, R.M.; Kosurkar, U.B.; Ramaiah, M.J.; Dadmal, T.L.; Pushpavalli, S.N.C.V.; Pal-Bhadra, M. Synthesis and biological evaluation of novel triazoles and isoxazoles linked 2-phenyl benzothiazole as potential anticancer agents. Bioorg. Med. Chem. Lett. 2012, 22, 5424–5427. [CrossRef]

133. Kamal, A.; Nagasheshadri, B.; Nayak, V.L.; Srinivasulu, V.; Sathish, M.; Kapure, J.S.; Reddy, S. Synthesis and biological evaluation of benzimidazole-oxindole conjugates as microtubule-targeting agents. Bioorg. Chem. 2015, 63, 72–84. [CrossRef]
134. Spadaro, A.; Frotscher, M.; Hartmann, R.W. Optimization of Hydroxybenzothiazoles as Novel Potent and Selective Inhibitors of 17β-HSD1. *J. Med. Chem.* 2012, 55, 2469–2473. [CrossRef]

135. Ge, J.-F.; Zhang, Q.-Q.; Lu, J.-M.; Kaiser, M.; Wittlin, S.; Brun, R.; Ihara, M. Synthesis of cyanine dyes and investigation of their in vitro antiprotzoal activities. *MedChemComm* 2012, 3, 1435–1442. [CrossRef]

136. Neumaier, B.; Deisenhofer, S.; Sommer, C.; Solbach, C.; Reske, S.N.; Mottaghy, F. Synthesis and evaluation of 18F-fluoroethylated benzothiazole derivatives for in vivo imaging of amyloid plaques in Alzheimer’s disease. *Appl. Radiat. Isot.* 2010, 68, 1066–1072. [CrossRef]

137. Dishino, D.D.; Welch, M.J.; Kilbourn, M.R.; Raichle, M.E. Relationship between lipophilicity and brain extraction of C-11-labeled radiopharmaceuticals. *J. Nucl. Med.* 1983, 24, 1030–1038.

138. Joule, J.A.; Mills, K. Quinolines and Isoquinolines. In *Heterocyclic Chemistry at a Glance*; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2012; pp. 62–70.

139. Al-Harthy, T.; Abdel-Jalil, R.; Zoghaib, W.; Pflüger, M.; Hofmann, E.; Hundsberger, H. Design and Synthesis of Benzothiazole Schiff Bases of Potential Antitumor Activity. *Heterocycles* 2016, 92, 1282–1292.

140. Al-Harthy, T.; Zoghaib, W.M.; Stoll, R.; Abdel-Jalil, R. Design, synthesis, and antimicrobial evaluation of novel 2-arylbenzothiazole analogs bearing fluorine and piperazine moieties. *Montatshefte Chem.—Chem. Mon.* 2018, 149, 645–651. [CrossRef]

141. Reddy, T.S.; Kulhari, H.; Reddy, G.; Bansal, V.; Kamal, A.; Shukla, R. Design, synthesis and biological evaluation of 1,3-diphenyl-1H-pyrazole derivatives containing benzimidazole skeleton as potential anticancer and apoptosis inducing agents. *Eur. J. Med. Chem.* 2015, 101, 790–805. [CrossRef] [PubMed]

142. Zawawi, N.K.N.A.; Taha, M.; Ahmat, N.; Wadood, A.; Ismail, N.H.; Rahim, F.; Ali, M.; Abdulllah, N.; Khan, K.M. Novel 2,5-disubstituted-1,3,4-oxadiazoles with benzimidazole backbone: A new class of b-glucuronidase inhibitors and in silico studies. *Bioorg. Med. Chem.* 2015, 23, 3119–3125. [CrossRef] [PubMed]

143. El-Abadelah, M.M.; Sabri, S.S.; Zarga, M.H.A.; Abdel-Jalil, R.J. Substituted benzimidazoles. Part I. Synthesis and properties of some 2-aryl-5-fluoro-6-(4-methyl-1-piperazinyl)-1H-benzimidazoles. *Heterocycles* 1995, 42, 2713–2728. [CrossRef]

144. Abdel-Jalil, R.J.; Voelter, W. Synthesis of new 2-ferrocenyl-5-fluoro-6-(4-substituted-1-piperazinyl)-1H-benzimidazoles of potential biological interest. *J. Heterocycl. Chem.* 2005, 42, 67–71. [CrossRef]

145. Abu-Elteen, K.H.; Abdel-Jalil, R.J.; Hamad, M.A.; Ghaleb, M.; Khan, K.M.; Voelter, W. Fungicidal effects of some derivatives of 2-ferrocenyl-benzimidazoles: A possible template for antifungal drug design. *J. Med. Sci.* 2008, 8, 673–681. [CrossRef]

146. Jauhari, P.K.; Bhavani, A.; Varalwar, S.; Singhal, K.; Raj, P. Synthesis of some novel 2-substituted benzoxazoles as anticancer, antifungal, and antimicrobial agents. *Med. Chem. Res.* 2008, 17, 412–424. [CrossRef]

147. Setoguchi, M.; Imura, S.; Sugimoto, Y.; Yoneda, Y.; Chiba, J.; Watanabe, T.; Muro, F.; Igo, Y.; Takayama, G.; Mika Yokoyama, A.; et al. Identification of trans-4-[1-[[7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazoyl] acetyl]-(4S)-fluoro-(2S)-pyrrolidinylmethoxy]cyclohexanecarboxylic acid as a potent, orally active VLA-4 antagonist. *Bioorg. Med. Chem. Lett.* 2012, 20, 1201–1212. [CrossRef]

148. Omori, N.; Kouyama, N.; Yukimasa, A.; Watanabe, K.; Yokota, Y.; Tanioka, H.; Nambu, H.; Yukioka, H.; Sato, N.; Tanaka, Y.; et al. Hit to lead SAR study on benzoxazole derivatives for an NPY Y5 antagonist. *Bioorg. Med. Chem. Lett.* 2012, 22, 2020–2023. [CrossRef]

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).