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Design and synthesis of some new zafirlukast tetrazole/piperazine scaffolds

V. Bala Yesu[1,2], D. Suresh Babu[1], K. Sajitha[1], K. Yelamanda Rao[3], K. Vamsi[4], V. Murali[1], A. G. Damu[3] and D. Srinivasulu[1]*

[1]Department of Chemistry, Sri Venkateswara University, Tirupati, Andhra Pradesh, India
[2]Department of Chemistry, SGK Government Degree College, Palnadu, Andhra Pradesh, India
[3]Department of Bioorganic Chemistry and Research, Yogi Vemana University, Kadapa, Andhra Pradesh, India
[4]Department of Chemistry, Indian Institute of Science Education and Research, Tirupati, Andhra Pradesh, India

ABSTRACT The present study reports the modification of **zafirlukast**, a clinically established cysteinyl leukotriene receptor antagonist, by incorporating tetrazole and piperazine moieties to enhance its therapeutic potential, particularly in the context of neurodegenerative diseases. The proposed structural modifications involve replacing the aromatic sulfonamide group with tetrazole and piperazine, aiming to retain the stability of the compound for improving its bioactivity. The synthesis of zafirlukast tetrazole/piperazine scaffolds (**10a-g**) was successfully carried out through a linear synthetic route, involving methylation, esterification, radical bromination, and subsequent coupling reactions, followed by reduction and amidation.

KEYWORDS Indole, Zafirlukast intermediate, Tetrazole, Piperazine, Carbamate.

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INTRODUCTION

Advancements in pharmaceutical chemistry have led to the development of novel therapeutic agents with improved efficacy and specificity. Achieving these advancements often requires modifying chemical structures through detailed analysis of pharmacological mechanisms and biological target interactions, which are crucial for enhancing the quality, safety, and therapeutic performance of new drug candidates.[1] In this context, heterocycles, cyclic compounds containing atoms of at least two different elements, have become indispensable scaffolds in medicinal chemistry due to their broad biological relevance.[2] Among these, fused Indole structures have emerged as essential motifs in drug discovery, with derivatives exhibiting a wide spectrum of biological activities, including antibiotic, anti-inflammatory, and anticancer properties.[3]

One notable example of a heterocyclic compound is zafirlukast, a cysteinyl leukotriene receptor antagonist that has been clinically used for over two decades in the treatment of asthma by mitigating bronchoconstriction and inflammation.[4] However, despite its established therapeutic efficacy, the profile of zafirlukast is limited by occasional hepatotoxicity. Recent studies, however, suggest that zafirlukast may also offer neuroprotective benefits, potentially providing new opportunities in the managing of neurodegenerative diseases over the reduction of oxidative stress and brain damage. This highlights the importance of structural modifications and the exploration of new pharmacological potentials in improving existing drug candidates.[5-7]

In parallel, tetrazole-containing moieties have gained considerable attention in drug design due to their bioisosteric properties, particularly their ability to mimic carboxylic acids. Tetrazole derivatives have demonstrated a broad range of therapeutic activities, including antiviral, anticancer, and neuroprotective effects. For example, cenobamate, a tetrazole-based compound, is currently being explored for its potential in treating neurological disorders such as Alzheimer's and Parkinson's diseases, emphasizing the growing importance of tetrazoles in the development of novel therapeutic agents.[8-10]

*Corresponding author: Email: doddaga_s@yahoo.com

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Similarly, piperazines, six-membered nitrogen-containing heterocycles, have established themselves as critical pharmacophores in medicinal chemistry. Piperazine moieties are integral to many bioactive compounds, including several commercially available fluoroquinolone antibiotics, such as norfloxacin, levofloxacin, and ciprofloxacin. The combination of piperazine with other heterocyclic systems, such as tetrazole, has shown promise in enhancing biological activity, particularly in antifungal research.[11,12]

Building on these advancements, this study seeks to explore the potential of zafirlukast analogs modified by incorporating tetrazole and piperazine moieties. Specifically, the replacement of the aromatic sulfonamide group in zafirlukast with tetrazole and piperazine is proposed as a strategy to augment its therapeutic efficacy, especially in the context of neurodegenerative diseases. Retaining the aromatic ring structure is essential to preserve potential π-π stacking interactions, which could enhance the stability and bioactivity of the modified compounds.[13] By leveraging the anti-inflammatory and neuroprotective properties of tetrazole and piperazine, these modified zafirlukast derivatives are anticipated to offer improved therapeutic outcomes, extending their utility beyond asthma treatment to include potential neurodegenerative indications. The present work outlines the design, synthesis, and structural characterization of these zafirlukast tetrazole/piperazine scaffolds anticipating as potential therapeutic agents.

RESULTS AND DISCUSSION

Synthesis

The synthesis of analogs **10a-g** was successfully achieved through a linear synthetic route with suitable modifications from a reported method.[14,15] Each step was carefully optimized to ensure efficiency and reproducibility. Briefly, the synthesis proceeds as follows. Initially, the process began with the methylation of 5-nitroindole (**1**) using methyl iodide, resulting in *N*-methyl-5-nitroindole (**2**). Esterification of compound **3** followed by radical bromination yielded building block **4** which was coupled with **2** to yield compound **5** under Ag_2O conditions. Subsequently, the nitro intermediate **5** was reduced with H_2 and Pd/C, yielding the aniline compound **6**, which serves as a key pre-cursor for further derivatization. Moreover, urethane (**7**) was obtained from intermediate **6** through a reaction with cyclopentyl chloroformate. Finally, the ester group was hydrolyzed to yield the corresponding acid, which was then reacted with various tetrazoles (**9a-d**) and piperazine hybrids (**9e-g**) to form the desired zafirlukast tetrazole/piperazine scaffolds (**10a-g**) in good yields.

The structures of the compounds **10a-g** were confirmed by spectral (Fourier transform infrared spectroscopy [FTIR], ^{1}H nuclear magnetic resonance [NMR], ^{13}C NMR, and high-resolution mass spectrometry [HRMS]) data. The FTIR spectra of compounds **10a-g** showed absorption bands at 3308–3054 cm^{-1} (-NH, amide), 2958–2925 cm^{-1} (-CH, amide), 1738–1720 cm^{-1} (C=O, carbamate), and 1720–1687 cm^{-1} (C=O, amide). The ^{1}H NMR spectra of the compounds exhibited chemical shifts in various regions. Aromatic protons resonated between δ 7.89 and 6.36, while the cyclopentyl oxygen-attached ring protons appear as a multiplet at δ 5.22–5.10. Methylene protons (between the indole and phenyl rings) were observed at δ 4.06–4.01. In addition, methoxy protons were detected at δ 3.93–3.87, and *N*-methyl protons appeared between δ 3.70 and 3.54. Finally, four methylene (-CH_2) protons were shown up as three multiplets in the range of δ 1.94–1.43, with a 1:2:1 intensity ratio. The ^{13}C NMR spectra showed distinct chemical shifts in the following regions: the carbonyl carbons of the carbamate and amide groups are observed between δ 171 and 156, the methoxy carbon appears at δ 55–50, and the *N*-methyl carbon is observed between δ 45 and 39 ppm. HRMS data revealed molecular ion peaks that corresponded to the molecular weights of the compounds.

EXPERIMENTAL SECTION

Chemicals were purchased from suppliers and used as received without further purification. Reactions were monitored by TLC, and the products were purified through column chromatography. FTIR spectra were obtained using a SHIMADZU-8,400 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-500 spectrometers. Tetramethyl silane served as the internal standard, with chemical shifts reported in parts per million (δ, ppm) and coupling constants in hertz (J = Hz). HRMS measurements were taken using a Xevo TQD Quadrupole mass spectrometer. Melting points were determined using an open capillary method with a GUNA melting point apparatus.

The syntheses of 1-methyl-5-nitro-1*H*-indole **(2),** methyl 4-(bromomethyl)-3-methoxybenzoate **(4),** methyl 3-methoxy-4-((1-methyl-5-nitro-1*H*-indol-3-yl)methyl) benzoate **(5)** and methyl 4-((5-amino-1-methyl-1*H*-indol-3-yl) methyl)-3-methoxybenzoate **(6)** were executed in strict adherence to the delineated experimental protocol.[14,15]

1-Methyl-5-nitro-1*H*-indole (2)

Literature m.p.: 167°C, observed m.p.: 167–169°C.

Methyl 4-(bromomethyl)-3-methoxybenzoate (4)

Literature m.p.: 92–94°C, observed m.p.: 96–99°C.

Methyl 3-methoxy-4-((1-methyl-5-nitro-1*H*-indol-3-yl)methyl)benzoate (5)

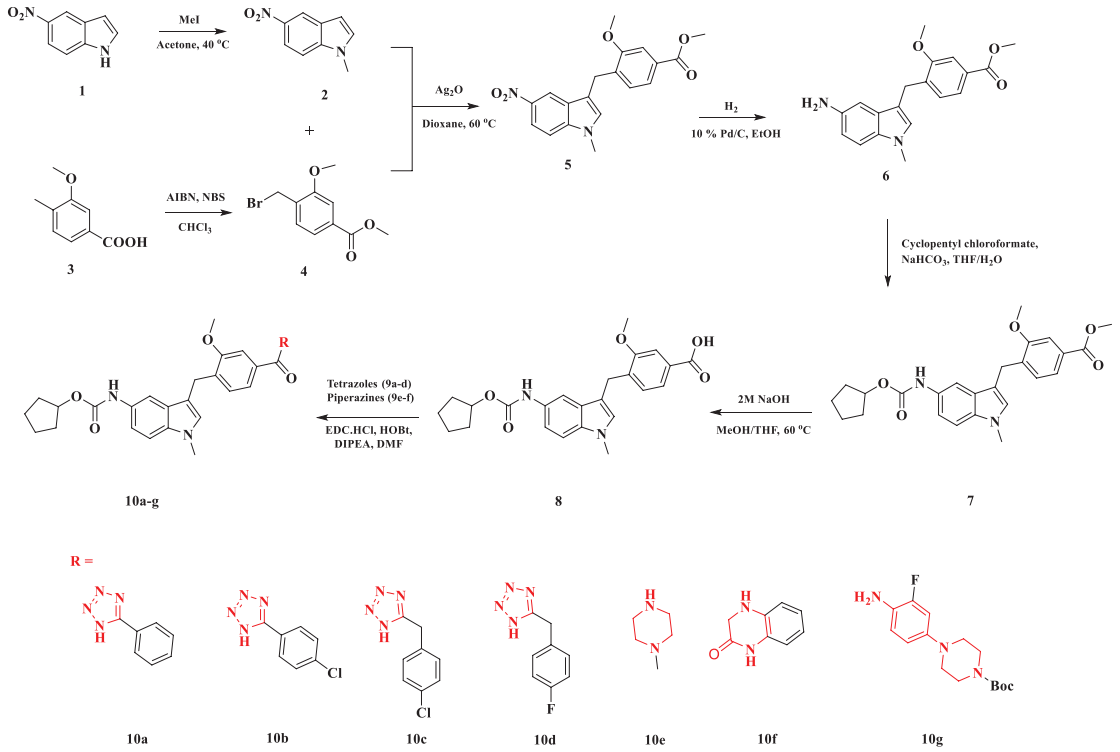
Literature m.p.: 149–150°C, observed m.p.: 152–154°C.

Methyl 4-((5-amino-1-methyl-1*H*-indol-3-yl) methyl)-3-methoxybenzoate (6)

Literature m.p.: 153–155°C, observed m.p.: 157–158°C.

Methyl 4-((5-(((cyclopentyloxy)carbonyl)amino)-1-methyl-1*H*-indol-3-yl)methyl)-3-methoxy benzoate (7)

Compound **6 (**6.1 mmol) was dissolved in tetrahydrofuran (THF), and N,N-diisopropylethylamine (DIPEA) was added. The mixture was cooled to 4°C, and cyclopentyl chloroformate (6.8 mmol) was added dropwise. The reaction was allowed to stir at room temperature for 4 h. Afterward,



Scheme 1: Synthesis of zafirlukast tetrazole/piperazine scaffolds (10a-g)

10 mL of 1% aqueous HCl was added, and the mixture was stirred for an additional 5 min. EtOAc (10 mL) was then added, and the phases were separated. The aqueous layer was extracted (2 × EtOAc). The combined organic layers were washed with 5 mL of brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to yield the desired compound **7.** Greyish solid; Yield: 64%; m.p.: 142–144°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.14 (s, 1H), 7.45 (s, 2H), 7.44 (dd, J = 7.9, 1.4 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 7.01 (dd, J = 8.7, 1.7 Hz, 1H), 6.66 (s, 1H), 5.12–5.06 (m, 1H), 3.94 (s, 2H), 3.80 (s, 3H), 3.72 (s, 2H), 3.63 (s, 3H), 1.72–1.61 (m, 7H), 1.56–1.48 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 167, 158, 154, 136, 133, 130, 129, 128, 127, 126, 124, 117, 114, 112, 109, 108, 78, 55, 52, 33, 32, 30, 23.

4-((5-(((Cyclopentyloxy)carbonyl)amino)-1-methyl-1*H*-indol-3-yl)methyl)-3-methoxybenzoic acid (8)

A solution of ester compound **7 (**4.5 mmol) in MeOH and THF (2:1) was treated with 2M NaOH. The mixture was stirred at 60°C until the ester was completely consumed, as monitored by TLC. Subsequently, 2M HCl was added, and the reaction mixture was washed (3 × EtOAc). The organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure using a rotary evaporator to yield compound **8**. White solid; Yield: 70%; m.p.: 132–136°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 12.86 (s, 1H), 7.58–7.31 (m, 4H), 7.22–7.03 (m, 3H), 6.98 (ddd, J = 9.0, 6.9, 1.0 Hz, 1H), 4.01 (s, 2H), 3.90 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 167, 158, 154, 136, 133, 130, 129, 128, 127, 126, 124, 117, 114, 112, 109, 108, 78, 55, 33, 32, 30, 23.

General procedure for the synthesis of zafirlukast tetrazole/piperazine scaffolds (10a-g)

To an ice-cooled solution of compound **8 (**7.1 mmol) in 5 mL of DMF, various tetrazole/piperazine compounds (7.4 mmol) were added along with hydroxybenzotriazole (HOBt, 10.6 mmol), (3-dimethylaminopropyl) ethylcarbodiimide hydrochloride (EDC·HCl, 14.2 mmol), and a few drops of (DIPEA, 17.75 mmol). The mixture was stirred at room temperature for 1 h. After completion, the reaction mixture was poured onto crushed ice, and the resulting precipitate was filtered, dried, and recrystallized from ethanol to yield the zafirlukast tetrazole/piperazine scaffolds (**10a-g**).

Cyclopentyl (3-(2-methoxy-4-(5-phenyl-1H-tetrazole-1-carbonyl)benzyl)-1-methyl-1H-indol-5-yl)carbamate (10a)

Off-white solid: Yield: 67%, m.p.: 189–191°C, FTIR (KBr, υ, cm^{-1}): 3054, 2969, 1738, 1708, 1422, 1264, 733; ^{1}H NMR (500 MHz, CDCl3, δ): 7.64–7.60 (m, 1H), 7.26 (s, 1H), 7.21–7.13 (m, 2H), 7.09–7.01 (m, 1H), 6.96–6.69 (m, 4H), 5.20–5.16 (m, 1H), 4.05–4.02 (t, 2H), 3.87 (s, 3H), 3.63 (s, 3H), 1.89–1.81 (m, 2H), 1.78–1.62 (m, 4H), 1.62–1.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 171, 157, 156, 134, 133, 130, 129, 128, 122, 117, 115, 113, 109, 108, 77, 76, 55, 52, 41, 32, 31, 25, 24, 23, 22, 20, 18, 14, 11; HRMS: Calc. for $C_{31}H_{30}N_6O_4$ 550.2312; found 551.3526 $[M+H]^+$.

Cyclopentyl (3-(4-(5-(4-chlorophenyl)-1H-tetrazole-1-carbonyl)-2-methoxybenzyl)-1-methyl-1H-indol-5-yl) carbamate (10b)

Pale pink solid; Yield: 67%; m.p.: 189–191°C; FTIR (KBr, υ cm^{-1}): 3054, 2970, 1738, 1720, 1422, 1264, 733; ^{1}H NMR (500 MHz, CDCl3, δ): 7.50 (s, 1H), 7.46 (t, 2H), 7.11–6.91 (m, 4H), 6.90–6.65 (m, 2H), 6.622 (d, 1H), 5.10

(m, 1H), 3.93 (d, 2H), 3.78 (s, 3H), 3.54 (s, 3H), 1.8–1.72 (m, 2H), 1.69–1.57 (m, 4H), 1.52–1.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 169, 156, 155, 133, 131, 130, 129, 128, 128, 127, 127, 121, 116, 114, 111, 110, 108, 107, 76, 75, 54, 51, 40, 31 31, 24, 23, 22, 17; HRMS: Calc. for $C_{31}H_{29}ClN_6O_4$ 584.1942; found 585.2011 $[M+H]^+$.

Cyclopentyl (3-(4-(5-(4-chlorobenzyl)-1H-tetrazole-1-carbonyl)-2-methoxybenzyl)-1-methyl-1H-indol-5-yl) carbamate (10c)

Brick red solid; Yield: 69%; m.p.: 189–191°C; FTIR (KBr, υ cm^{-1}): 3054, 2970, 1738, 1701, 1422, 1264, 733; ^{1}H NMR (500 MHz, CDCl3, *δ*): 7.60 (m, 1H), 7.57–7.53 (m, 2H), 7.25 (s, 1H), 7.16–7.14 (m, 2H), 7.12–7.03 (m. 2H), 6.99–6.82 (m, 2H), 6.79–6.65 (s, 2H), 5.21–5.17 (m, 1H), 4.06–4.02 (t, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 1.90–1.84 (m, 2H), 1.79–1.68 (m, 4H), 1.62–1.50 (m, 2H); ^{13}C NMR (125 MHz, CDCl3, *δ*): 171, 157, 157, 135, 134, 131, 130, 129, 128, 122, 121, 119, 117, 115, 112, 112, 111, 109, 108, 77, 77, 77, 76, 55, 52, 41, 35, 34, 33, 32, 31, 29, 25, 24, 23, 22, 21, 20, 18, 14, 12, 11; HRMS: Calc. for $C_{32}H_{31}ClN_6O_4$ 598.2108; found 599.1738 $[M+H]^+$.

Cyclopentyl (3-(4-(5-(4-fluorobenzyl)-1H-tetrazole-1-carbonyl)-2-methoxybenzyl)-1-methyl-1H-indol-5-yl) carbamate (10d)

Pale red solid; Yield: 65%; m.p.: 192–194°C; FTIR (KBr, υ cm^{-1}): 3054, 2970, 1738, 1720, 1422, 1264, 733; ^{1}H NMR (500 MHz, CDCl3, *δ*): 7.50 (s, 1H), 7.46 (t, 2H), 7.11–6.94 (m, 4H), 6.90–6.65 (m, 2H), 6.62 (d, 1H), 5.10 (dt, 1H), 4.17 (s, 2H), 3.93 (d, 2H), 3.78 (s, 3H), 3.54 (s, 3H), 1.82–1.72 (m, 2H), 1.69–1.57 (m, 4H), 1.52–1.43 (m, 4H); ^{13}C NMR (125 MHz, CDCl3, *δ*): 170, 156, 155, 133, 131, 130, 129, 128, 128, 127, 121, 117, 114, 119, 112, 110, 108, 107, 76, 76, 76, 54, 52, 40, 32, 31, 24, 23, 22, 17, 11; HRMS: Calc. for $C_{32}H_{31}FN_6O_4$ 582.2418; found 583.3422 $[M+H]^+$.

Cyclopentyl (3-(2-methoxy-4-(4-methylpiperazine-1-carbonyl)benzyl)-1-methyl-1H-indol-5-yl)carbamate (10e)

Pale pink solid; Yield: 66%; m.p.: 191–196°C; FTIR (KBr, υ cm^{-1}): 3054, 2970, 1738, 1422, 1264, 733; ^{1}H NMR (500 MHz, *δ*): 7.57–7.52 (m, 1H), 7.26 (s, 1H), 7.20–7.13 (m, 2H), 7.08–7.07 (d, 1H), 6.95–6.92 (m, 2H), 6.83–6.79 (m, 1H), 6.75 (m, 1H), 6.56–6.54 (s, 1H), 5.22–5.18 (m, 2H), 4.06–4.03 (s, 3H), 3.88 (s, 3H), 3.70 (s, 3H), 2.47–2.32 (m, 1H), 1.93–1.84 (m, 2H), 1.79–1.71 (m, 4H), 1.65–1.55 (m, 2H); ^{13}C NMR (125 MHz, CDCl3, *δ*): 171, 157, 134, 133, 132, 130, 129, 128, 127, 119, 113, 109, 108, 77, 76, 55, 46, 33, 32, 25, 23; HRMS: Calc. for $C_{29}H_{36}N_6O_4$ 504.2703; found 505.2697 $[M+H]^+$.

Cyclopentyl (3-(2-methoxy-4-(3-oxo-1,2,3,4-tetrahydroquinoxaline-1-carbonyl)benzyl)-1-methyl-1H-indol-5-yl)carbamate (10f)

Pale red solid; Yield: 73%; m.p.: 194–196°C; FTIR (KBr, υ cm^{-1}): 3054, 2968, 1732, 1687 1493, 1421 1264, 733; ^{1}H NMR (500 MHz, CDCl3, *δ*): 8.33 (s, 1H), 7.89–7.87 (m, 1H), 7.62–7.50 (m, 3H), 7.41–7.33 (m, 1H), 7.20–7.16 (m, 2H), 7.10–7.06 (m, 1H), 6.96–6.78 (m, 1H), 6.74–6.71 (m, 1H), 6.60–6.54 (m, 1H), 5.21–5.18 (m, 1H), 4.04–4.01 (t, 2H), 3.87 (s, 3H), 3.68 (s, 3H), 1.88–1.86 (m, 2H), 1.78–1.74 (m, 4H), 1.59–1.52 (m, 2H); ^{13}C NMR (125 MHz, CDCl3, *δ*): 169, 165, 157, 153, 136, 133, 132, 131, 130, 128, 127, 126, 125, 123, 120, 118, 116, 113, 110, 109, 108, 78, 55, 46, 32, 32, 30, 23; HRMS: Calc. for $C_{32}H_{32}N_4O_5$ 552.1943; found 553.6478 $[M+H]^+$.

Tert-butyl 4-(4-(4-((5-(((cyclopentyloxy)carbonyl)amino)-1-methyl-1H-indol-3-yl)methyl)-3-methoxybenzamido)-3-fluorophenyl)piperazine-1-carboxylate (10g)

Pink solid; Yield: 75%; m.p.: 189–191°C; FTIR (KBr, υ cm^{-1}): 3308, 3054, 2970, 1738, 1683, 1587, 1422, 1264, 733; ^{1}H NMR (500 MHz, CDCl3, *δ*): 8.48 (s, 1H), 7.59–7.55 (m, 2H), 7.38 (s, 1H), 7.28–7.26 (m, 1H), 7.17–7.01 (m, 4H), 6.86–6.71 (m, 3H), 6.43–6.36 (m, 1H), 5.19–5.14 (m, 1H), 4.03–4.02 (t, 2H), 3.85 (s, 3H), 3.68 (s, 3H), 3.59–3.5 (m, 4H), 2.98–2.87 (m, 4H), 1.87–1.80 (m, 2H), 1.75–1.64 (m, 4H), 1.61–1.52 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, CDCl3, *δ*): 164, 156, 155, 155, 154, 153, 152, 151, 141, 140, 134, 133, 132, 131, 129, 128, 127, 126, 125, 120, 119, 118, 117, 116, 114, 113, 111, 109, 108, 107, 106, 102, 101, 78, 77, 75, 74, 53, 50, 49, 48, 39, 31, 30, 26, 23, 21; HRMS: Calc. for $C_{39}H_{46}FN_5O_6$ 699.8210; found 701.2409 $[M+H]^+$.

CONCLUSION

A new series of zafirlukast analogs (**10a-g)** were synthesized by modifying with tetrazole and piperazine moieties, aimed to enhance the therapeutic potential of the parent compound. By replacing the aromatic sulfonamide group of zafirlukast with tetrazole and piperazine, these new compounds may have promising bioactivity. The impact of this study lies in its potential to expand the therapeutic scope of **zafirlukast**, mostly in the context of neurodegenerative diseases, such as Alzheimer's and Parkinson's. By laying the groundwork for the development of multitarget therapeutic agents, this research opens new possibilities for treating complex, multi-faceted diseases, and future studies will be crucial for unlocking their full therapeutic potential.

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