(Benzylideneamino)triazole–Thione Derivatives of Flurbiprofen: An Efficient Microwave-Assisted Synthesis and In Vivo Analgesic Potential

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ABSTRACT: Triazole is an imperative heterocycle renowned for its broad-spectrum biological significance. In this manuscript, facile microwave-assisted synthesis of a series of 4-(benzyldieneamino)-3-(1-(2-fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione 6(a–m) derivatives along with their in vivo analgesic activity is reported. 2-(2-Fluoro-[1,1′-biphenyl]-4-yl)propanoic acid (flurbiprofen) was converted to methyl 2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanoate using microwave irradiation, followed by its hydrazinolysis with hydrazine monohydrate. 2-(2-Fluoro-[1,1′-biphenyl]-4-yl)propanohydrazide thus obtained was converted to 4-amino-3-(1-(2-fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione, followed by its condensation with different aromatic aldehydes to get the title compounds. Structures of all the synthesized compounds were established using different methods (1H NMR and 13C NMR spectroscopies, mass spectrometry, and elemental analysis) and evaluated for their potential as analgesic agents by tail flick, hot plate, and writhing methods. The results of this in vivo study revealed several compounds as potent analgesic agents among which compound 6e showed significant analgesic effect for all the three assays employed.

1. INTRODUCTION

Synthesis of triazoles and their biological importance have received considerable attention in recent years, and this class of compounds have become one of the potential agents for drug discovery.1–5 Among these, 1,2,4-triazoles represent an important class of organic compounds with wide use in medicine, agriculture, and industry.6 A wide variety of therapeutically interesting drug candidates possessing analgesic, anti-inflammatory, anti-microbial, anti-cancer, anti-depressant, anti-fungal, anti-convulsant, and anti-viral activities are discussed in the literature possessing the 1,2,4-triazole moiety.6–16

Many strategies have been reported in the literature regarding the development of more effective NSAIDs (non-steroidal anti-inflammatory drugs) with reduced side effects.17–19 In certain cases, derivatization of the carboxylic functional group in NSAIDs led to increased analgesic and anti-inflammatory activities with reduced ulcerogenic potential.20,21

Flurbiprofen, 2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanoic acid, is a non-selective cyclooxygenase (COX) inhibitor for the treatment of non-infectious inflammation, arthritis, and pain.22–24 However, like other drugs of this category, it is also associated with gastro-intestinal (GI) ulceration, nephrotoxicity, and bleeding.25,26 Keeping in view the analgesic activities of flurbiprofen and 1,2,4-triazoles, both the moieties are synergized in one hybrid unit as part of our ongoing program regarding the development of biologically active heterocycles. Flurbiprofen was esterified, followed by its hydrazinolysis, and subsequent reactions with carbon disulfide and hydrazine hydrate resulted in 4-amino-3-(1-(2-fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione (5). It was further reacted with different aldehydes to get a series of 4-(benzyldieneamino)-3-(1-(2-fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thiones 6(a–m) (Scheme 1). Besides chemical characterization, these compounds were checked for their analgesic activity on albino mice using tail flick, hot plate, and writhing methods.

2. RESULTS AND DISCUSSION

2.1. Chemistry. 4-Amino-3-(1-(2-fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione (5), the main inter-
mediate of the designed scheme, was synthesized using the multi-step synthesis strategy. Esterification of 2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanoic acid (1) using microwaves followed by hydrazinolysis yielded 2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanehydrazide (3).27 The use of microwaves in the esterification and hydrazinolysis steps plays a significant role as it assists in minimizing the reaction time and increases the yield of reactions.28,29 During this study, the reaction yield improved from 82 to 98.81% for the esterification step, while 74.94 to 95.12% for the hydrazinolysis reaction. 2-(2-Fluoro-[1,1′-biphenyl]-4-yl)propanehydrazide (3) was converted to potassium 2-(2-(2-fluoro-1-[1,1′-biphenyl]-4-yl)propanoyl)hydrazinecarbodithioate (4) with the reaction of carbon disulfide and potassium hydroxide, followed by its reaction with hydrazide hydrate to form 4-amino-3-(1-(2-fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione (5), followed by its condensation with different aldehydes under microwaves to get the title compounds. The use of microwaves in the condensation reactions was found more effective to attain better product yields and shorter reaction times (Table 1).

Structures of synthesized compounds 6(a–m) were confirmed through spectroscopic techniques and were found in agreement with the expected values. In 1H NMR spectra, the NH proton of the triazole ring appeared as a singlet around 14.00 ppm, whereas the imine N=CH proton emerged as a singlet near 9.20–10.78 ppm. Methyl (CH3) protons exhibited a doublet near 1.65 ppm and the methine (CH) proton gave a quartet around 4.40–4.65 ppm. Aromatic ring protons appeared between 6.76 and 8.34 ppm depending on their environment. In 13C NMR spectra, methyl carbon (CH3) and methine carbon (CH) appeared around 19.5 and 35.8 ppm individually. Thione carbon (C=S) was observed above 160.0 ppm and imine carbon (N=CH) near 153–154 ppm in all the synthesized derivatives 6(a–n). FT-IR data, elemental analysis results, and mass spectra too were in accordance with the structures of all the compounds.
2.2. Stereochemistry and X-ray Crystallography. A single crystal of 4-(benzylideneamino)-3-(1-(2-fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione (6a) as a representative of the title series of compounds 6(a–m) was grown in 90% ethanol and examined by single-crystal X-ray diffraction. The data shows that the C=N bond exhibits the E configuration. It is evident from the crystal data that sulfur exists in the thione form instead of thiol (Figure 1). Molecules form H-bonded dimers via pairs of centrosymmetric N–H⋯S interactions (Figure 2). A planar conformation between the benzylidene-amino and triazole moieties is stabilized via a C–H⋯S interaction. F⋯F interactions at 2.871 Å and C–H⋯F interactions give rise to an overall 3D supramolecular network. Crystal data and structure refinement details are given in the Experimental Section.

2.3. Analgesic Activity. The newly synthesized 4-(benzylideneamino)-3-(1-(2-fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thiones 6(a–m) were evaluated for their analgesic activities by three different methods, that is, tail flick, hot plate, and writhing methods. Albino mice for the current studies were housed and kept at the animal house situated at the University College of Pharmacy in the University of the Punjab Lahore, Pakistan, in groups of six and were acclimatized to experimental conditions for 2 days. Water was freely provided to the animals while access to feed was withdrawn 1 day before the experiments.

2.3.1. Tail Flick Method. Compounds 6(a–m) were tested for their analgesic activity using the tail flick method.30,31 This method is based on the phenomenon that certain drugs such as morphine can selectively prolong the duration of distinctive tail withdrawal reflex time when the distal end of mouse's tail is immersed in water at 55 ± 1.0 °C. Test compounds were assessed at equimolar oral doses relative to 10 mg/kg of flurbiprofen. Using this method, the analgesia effect was calculated for 0.5 to 4.5 h period since it was found that most of the animals showed analgesia ranging from 1 to 3 h. Moderate to significant activities for all the synthesized derivatives were observed, which are shown in Table 2 along with the analgesic activity of reference standard, flurbiprofen. Among the 14 tested compounds, 6e, 6i, 6j, and 6m showed highly significant analgesic activity compared with the reference drug, while compounds 6b, 6d, and 6g showed significant analgesic activities. Compounds 6a, 6f, and 6l showed less to moderately significant analgesic activities, while 6c, 6h, and 6k showed the least activity compared with the reference drug (Figure 3).

2.3.2. Hot Plate Method. The title compounds 6(a–m) were also evaluated for analgesic activity by using the hot plate method.32,33 Compounds were tested at equimolar oral dose relative to 10 mg/kg flurbiprofen. The analgesia effect was checked from 0.5 to 4.5 h period, and it was found that most of the animals showed analgesia ranging from 0.5 to 3.5 h. Results showed moderate to significant analgesic activities for the test compounds 6(a–m) and are shown in Table 3 compared with flurbiprofen (reference standard). Compounds 6c, 6i, 6l, and 6m showed highly significant analgesic activities compared with the reference drug, while 6a, 6h, and 6j exhibited moderate activities. The analgesic effects by the hot plate method are depicted in Figure 4.

2.3.3. Acetic Acid Induced Writhing Method. The analgesic activity by the acetic acid induced writhing method was studied on the title compounds.34,35 Albino mice were kept in the test cage for half an hour for acclimatization to the environment before acetic acid injection. Animals were dosed orally (10 mg per kg body mass) with the test compounds and flurbiprofen (reference drug), and the analgesia effect was checked for the first half hour due to the fact that these compounds were found active in this time range. The percentage inhibition in the writhing method was calculated in two phases: the first phase during the initial 15 min after dose administration and the second phase for the next 15 min (16th–30th minute). Compounds 6a, 6e, and 6l exhibited highly significant analgesic activities while 6b, 6i, 6j, 6m, and 6h were found moderately active compared with the reference standard drug (Table 4). Compounds 6c, 6d, 6f, 6g, and 6k were found to possess comparable analgesic activities to the reference drug, flurbiprofen, and this is depicted in Figure 5. All the title compounds exhibited higher activity than the standard drug flurbiprofen. It was further noted that the percentage inhibition of all the compounds increased in the second half of the trial time (from 16th minute to 30th minute) compared with the first half (1st to 15th minute).

An insight into the structure–activity relationship indicates that compounds bearing a substituent at the ortho or para positions of the phenyl ring (2-hydroxy, 4-nitro, 4-N,N-dimethylamino) attached to the triazole heterocycle are more...
Table 2. Evaluation of the Analgesic Activity of 6(a−f) using the Tail Flick Method

| Compound ID | 0 h | 0.5 h | 1 h | 1.5 h | 2 h | 2.5 h | 3 h | 4 h | 4.5 h |
|-------------|-----|-------|-----|-------|-----|-------|-----|-----|-------|
| 6a          | 2.97 ± 0.197 | 2.91 ± 0.293 | 3.17 ± 0.289 | 3.48 ± 0.450 | 3.57 ± 0.419 | 3.59 ± 0.395 | 3.68 ± 0.380 | 3.97 ± 0.244 | 4.21 ± 0.234 |
| 6b          | 2.70 ± 0.072 | 2.66 ± 0.071 | 2.85 ± 0.080 | 3.01 ± 0.094 | 3.12 ± 0.098 | 3.17 ± 0.098 | 3.28 ± 0.100 | 3.50 ± 0.080 | 3.71 ± 0.070 |
| 6c          | 2.79 ± 0.081 | 2.75 ± 0.080 | 2.94 ± 0.087 | 3.06 ± 0.095 | 3.18 ± 0.099 | 3.24 ± 0.101 | 3.36 ± 0.104 | 3.57 ± 0.100 | 3.77 ± 0.104 |
| 6d          | 2.83 ± 0.105 | 2.78 ± 0.104 | 2.91 ± 0.108 | 3.04 ± 0.112 | 3.17 ± 0.116 | 3.24 ± 0.119 | 3.37 ± 0.120 | 3.58 ± 0.118 | 3.78 ± 0.118 |
| 6e          | 2.92 ± 0.116 | 2.87 ± 0.116 | 3.01 ± 0.120 | 3.15 ± 0.124 | 3.29 ± 0.128 | 3.37 ± 0.130 | 3.50 ± 0.132 | 3.71 ± 0.132 | 3.92 ± 0.132 |
| 6f          | 2.95 ± 0.127 | 2.90 ± 0.127 | 3.04 ± 0.131 | 3.18 ± 0.135 | 3.32 ± 0.139 | 3.40 ± 0.140 | 3.53 ± 0.142 | 3.74 ± 0.142 | 3.95 ± 0.142 |

3. CONCLUSIONS

Urged by the well-established analgesic properties of triazoles, a distinguished analgesic drug flurbiprofen was derivatized to obtain a series of novel 4-((benzylideneamino)-3-((2-fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thiones 6(a−m) by a facile microwave-assisted method in excellent yields. Facilitation of microwave irradiation during the core steps of synthesis was found reasonably effective in achieving better product yields and purities. Reaction times for the condensation reactions were significantly reduced by microwave irradiations as compared with the conventional heating method. The successful synthesis of the title compounds was validated from spectroscopic techniques and elemental analyses. The analgesic potential of the synthesized (benzylideneamino)triazole-thione derivatives of flurbiprofen was investigated in vivo by employing three different protocols. All the derivatives exhibited analgesic activity to a different degree; however, 6e displayed significant analgesic potential as a result of all the three assays. These experiments revealed that the compounds under study possess prospective analgesic activities and may serve as an architype for forthcoming studies through further derivatization and/or structural alteration.

4. EXPERIMENTAL SECTION

4.1. Apparatus, Reagents, and Chemicals. Chemicals employed in the research work were purchased from Wako and E. Merck and were used as received. Solvents were purified through standard procedures before use. Fourier transform infrared (FT-IR) spectroscopy spectra were scanned on a Thermo Nicolet IR 200 spectrometer, while an LCQ Advantage Max Thermo Fisher instrument was used in the ESI mode for mass spectra. 1H NMR spectra were recorded on a Bruker AVANCE-III 400 MHz spectrometer using TMS as the internal standard and 13C NMR spectra were recorded at 101 MHz. Melting points were determined on a Gallenkamp instrument and are uncorrected. For microwave-assisted reactions, a customized microwave oven (Orient eNNe781JF) equipped with inverter technology (for realistic control of the microwaves) operating at multiples of 100 W up to 1000 W generating 2450 MHz frequency was used. The temperature of the microwave-assisted reactions was monitored by Redington 9975-IRT gun. Crystal data were collected on a Bruker APEX 2 CCDC diffractometer using graphite-monochromated Mo Kα radiation.

4.2. General Procedures for Synthesis. Compounds 2 and 3 were synthesized by using our reported methods.27

4.2.1. 4-Amino-3-(1-(2-Fluoro-[1,1′-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione (5). A mixture of 2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanol (3) (0.500 g; 1.93 mmol), potassium hydroxide (0.108 g; 1.93 mmol), and carbon disulfide (0.147 g; 0.117 mL; 1.93 mmol) dissolved in ethanol (25 mL) was agitated for 16 h at room temperature. Ether was added to the mixture and the precipitated potassium 2-(2-[(2-fluoro-[1,1′-biphenyl]-4-yl)propanoyl]-hydrazinecarbodithioate (4) was collected by filtration. It was active as analgesic agents. Chloro and methoxy analogues exhibited significant activities regardless of their position on the phenyl ring (3-chloro, 4-chloro, 2,4-dichloro and 3,4-dimethoxy substituted derivatives), while the fluoro substituent seems to have no role in analgesic activity as the analogue came out to be least active.
then washed with ether and dried under vacuum. The filtered precipitates thus obtained (0.500 g) were dissolved in hydrazine hydrate 20% (6 mL) and reacted under microwaves for 30 min until complete evolution of hydrogen sulfide. Dilute acetic acid (50 mL; 0.1%) was added to the resultant solution to get white precipitates, which were crystallized from ethanol; mp 196 °C; IR (KBr) cm\(^{-1}\): 3314, 3140, 1265; \(^1\)H NMR (DMSO-\(\text{d}_6\), 400 MHz): \(\delta\) 1.58 (d, \(J = 7.2 \text{ Hz}, 3\text{H}, \text{CH}_3\)), 4.44 (q, \(J = 7.2 \text{ Hz}, 1\text{H}, \text{CH}\)), 5.48 (s, 2H, NH\(_2\)), 7.17–7.26 (m, 2H, ArH\(_2\)), 7.32–7.42 (m, 2H, ArH\(_2\)), 7.45–7.56 (m, 4H, ArH\(_2\)), 13.65 (s, 1H, NH ppm); \(^1^3\)C NMR (DMSO-\(\text{d}_6\), 101 MHz): \(\delta\) 19.5, 34.9, 115.3 (d, \(J = 23.2 \text{ Hz}\)), 123.9 (d, \(J = 3.0 \text{ Hz}\)), 126.8 (d, \(J = 14.1 \text{ Hz}\)), 127.9, 128.7, 128.8 (d, \(J = 3.0 \text{ Hz}\)), 130.9 (d, \(J = 4.0 \text{ Hz}\)), 135.0, 143.4 (d, \(J = 8.1 \text{ Hz}\)), 154.2, 159.0 (d, \(J = 246.4 \text{ Hz}\)), 166.4 ppm; Anal. Calc. for C\(_{23}\)H\(_{19}\)FN\(_4\)S: C, 68.23; H, 4.76; N, 13.92. Found: C, 68.23; H, 4.76; N, 13.92.

4.2.2. General Procedure for the Synthesis of \(4-(\text{Benzylideneamino})-3-(1-(2\text{-fluoro-[1,1\prime-biphenyl]-4-yl})-ethyl)-1\text{-H}-1,2,4-triazole-5(4H)-thione (6a)\). A mixture of 4-amino-3-(1-(2-fluoro-[1,1\prime-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione (5) (200 mg; 0.774 mmol), aromatic aldehyde (0.774 mmol), ethanol (25 mL), and glacial acetic acid (1–2 drops) was irradiated to reflux under microwaves till completion of the reaction. After removal of excess ethanol under vacuum, the contents were neutralized with ice-cooled aqueous sodium bicarbonate solution (4% w/w). The products were filtered and recrystallized from alcohol.

4.2.2.1. \((E)-4-(\text{Benzylideneamino})-3-(1-(2\text{-fluoro-[1,1\prime-biphenyl]-4-yl})ethyl)-1\text{-H}-1,2,4-triazole-5(4H)-thione (6a)\). White crystalline powder; mp 213 °C; IR (KBr) cm\(^{-1}\): 3083, 1579, 1219; \(^1\)H NMR (DMSO-\(\text{d}_6\), 400 MHz): \(\delta\) 1.65 (d, \(J = 6.8 \text{ Hz}, 3\text{H}, \text{CH}_3\)), 4.55 (q, \(J = 6.8 \text{ Hz}, 1\text{H}, \text{CH}\)), 7.20 (dd, \(J = 8.0 \text{ Hz}, 1.2 \text{ Hz}, 1\text{H}, \text{ArH}\)), 7.26 (dd, \(J = 11.6 \text{ Hz}, 1.2 \text{ Hz}, 1\text{H}, \text{ArH}\)), 7.39 (t, \(J = 6.4 \text{ Hz}, 1\text{H}, \text{ArH}\)), 7.44–7.62 (m, 8H, ArH\(_2\)), 7.83 (d, \(J = 7.2 \text{ Hz}, 2\text{H}, \text{ArH}\)), 9.90 (s, 1H, N=CH\(_2\)), 14.02 (s, 1H, NH ppm); \(^1^3\)C NMR (DMSO-\(\text{d}_6\), 101 MHz): \(\delta\) 19.6, 35.8, 115.7 (d, \(J = 23.2 \text{ Hz}\)), 124.3 (d, \(J = 3.3 \text{ Hz}\)), 127.2 (d, \(J = 13 \text{ Hz}\)), 128.3, 128.9, 129.0, 129.1 (d, \(J = 3.0 \text{ Hz}\)), 129.6, 131.3 (d, \(J = 4.0 \text{ Hz}\)), 133.1, 132.6, 135.2, 143.7 (d, \(J = 8.1 \text{ Hz}\)), 153.4, 159.3 (d, \(J = 247.5 \text{ Hz}\)), 162.1, 163.6 ppm; Anal. Calc. for C\(_{23}\)H\(_{19}\)FN\(_4\)S: C, 68.63; H, 4.76; N, 13.92. Found: C, 68.23; H, 4.75; N, 13.89. MS m/z: [M + H]\(^+\) 403.20.

4.2.2.2. \((E)-(2\text{-Chlorobenzylidene})amino)-3-(1-(2\text{-fluoro-[1,1\prime-biphenyl]-4-yl})ethyl)-1\text{-H}-1,2,4-triazole-5(4H)-thione (6b)\). Yellow crystalline powder; mp 189 °C; IR (KBr) cm\(^{-1}\): 3058, 1582, 1222; \(^1\)H NMR (DMSO-\(\text{d}_6\), 400 MHz): \(\delta\) 1.64 (d, \(J = 7.2 \text{ Hz}, 3\text{H}, \text{CH}_3\)), 4.60 (q, \(J = 7.2 \text{ Hz}, 1\text{H}, \text{CH}\)), 7.21 (dd, \(J = 8.0, 1.6 \text{ Hz}, 1\text{H}, \text{ArH}\)), 7.28 (dd, \(J = 11.9, 1.7 \text{ Hz}, 1\text{H}, \text{ArH}\)), 7.32–7.52 (m, 7H, ArH\(_2\)), 7.55–7.64 (m, 2H, ArH\(_2\)), 8.02 (d, \(J = 7.6 \text{ Hz}, 1\text{H}, \text{ArH}\)), 10.72 (s, 1H, N=CH\(_2\)), 14.08 (s, 1H, NH); \(^1^3\)C NMR (DMSO-\(\text{d}_6\), 101 MHz): \(\delta\) 19.3, 35.4, 115.3 (d, \(J = 23.2 \text{ Hz}\)), 123.9, 126.9 (d, \(J = 14.1 \text{ Hz}\)), 127.6, 127.9, 128.0, 128.7, 128.8 (d, \(J = 3.0 \text{ Hz}\)), 130.0, 130.4, 131.0 (d, \(J = 3.0 \text{ Hz}\)), 134.1, 134.8, 135.2, 143.5 (d, \(J = 8.1 \text{ Hz}\)), 153.4, 156.4, 159.0 (d, \(J = 247.5 \text{ Hz}\)), 161.7 ppm; Anal. Calc. for C\(_{23}\)H\(_{19}\)ClFN\(_4\)S: C, 63.22; H, 4.15; N, 12.82. Found: C, 63.23; H, 4.16; N, 12.79; MS m/z: [M + H]\(^+\) 437.58.

Figure 3. Analgesic activity by the tail flick method.
## Table 3. Evaluation of the Analogous Activity of the Synthetic Derivatives with the Hot Plate Method

| Compound ID | Hot plate time (min) | Variation of hot plate time with ± SDM (time in sec at 55 ± 1 °C) |
|-------------|----------------------|------------------------------------------------------------------|
| 6a          | 0 h                  | 6.98 ± 0.763                                                     |
| 6b          | 0.5 h min            | 6.95 ± 0.013                                                     |
| 6c          | 3 h                  | 6.82 ± 0.912                                                     |
| 6d          | 1 h                  | 6.58 ± 0.046                                                     |
| 6e          | 1.5 h                | 6.44 ± 0.168                                                     |
| 6f          | 2 h                  | 6.32 ± 0.188                                                     |
| 6g          | 2.5 h                | 6.28 ± 0.118                                                     |
| 6h          | 3.5 h                | 6.19 ± 0.118                                                     |
| 6i          | 4.5 h                | 6.08 ± 0.095                                                     |

### Compound 6e

- **C23H19FN4OS**: C, 66.01; H, 4.58; N, 13.39. Found: C, 65.99; H, 4.58; N, 13.45.

- **IR (KBr) cm⁻¹**: 3094, 1536, 1212. ¹H NMR (DMSO-d₆, 400 MHz): δ 1.65 (d, J = 7.2 Hz, 3H, CH₃), 4.62 (q, J = 7.2 Hz, 1H, CH), 7.23 (dd, J = 8.0 Hz, 1H, ArH), 7.35–7.50 (m, 6H, ArH), 7.61 (dd, J = 8.4 Hz, 1H, ArH), 7.83 (dd, J = 2.0 Hz, 1H, ArH), 8.05 (d, J = 8.4 Hz, 1H, ArH), 10.78 (s, 1H, N=CH), 14.09 (s, 1H, NH) ppm. ¹³C NMR (DMSO-d₆, 101 MHz): δ 19.7, 35.7, 115.6 (d, J = 24.2 Hz), 124.3 (d, J = 3.0 Hz), 127.3 (d, J = 14.1 Hz), 128.3, 128.8, 129.0, 129.1, 129.2 (d, J = 3.0 Hz), 129.5, 130.3, 131.4 (d, J = 4.0 Hz), 135.2, 136.3, 138.2, 143.8 (d, J = 8.1 Hz), 153.8, 155.3, 159.4 (d, J = 24.7 Hz), 162.0 ppm. Anal. Calcd for C₂₃H₁₉FN₄O₅S: C, 68.60; H, 3.64; N, 11.89. Found: C, 68.60; H, 3.65; N, 11.92; MS m/z: [M + H]⁺ 472.18.

### Compound 6h

- **C₂₃H₂₁F₂N₄O₅S**: C, 58.60; H, 3.64; N, 11.89. Found: C, 58.63; H, 3.65; N, 11.92; MS m/z: [M + H]⁺ 471.00.

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### Compound 6f

- **Yellow powder; mp 204 °C IR (KBr) cm⁻¹: 3094, 1536, 1212. ¹H NMR (DMSO-d₆, 400 MHz): δ 1.65 (d, J = 7.2 Hz, 3H, CH₃), 4.62 (q, J = 7.2 Hz, 1H, CH), 7.23 (dd, J = 8.0 Hz, 1H, ArH), 7.35–7.50 (m, 6H, ArH), 7.61 (dd, J = 8.4 Hz, 1H, ArH), 7.83 (dd, J = 2.0 Hz, 1H, ArH), 8.05 (d, J = 8.4 Hz, 1H, ArH), 10.78 (s, 1H, N=CH), 14.09 (s, 1H, NH) ppm. ¹³C NMR (DMSO-d₆, 101 MHz): δ 19.7, 35.7, 115.6 (d, J = 24.2 Hz), 124.3 (d, J = 3.0 Hz), 127.3 (d, J = 14.1 Hz), 128.3, 128.8, 129.0, 129.1, 129.2 (d, J = 3.0 Hz), 129.5, 130.3, 131.4 (d, J = 4.0 Hz), 135.2, 136.3, 138.2, 143.8 (d, J = 8.1 Hz), 153.8, 155.3, 159.4 (d, J = 24.7 Hz), 162.0 ppm. Anal. Calcd for C₂₃H₂₁F₂N₄O₅S: C, 58.60; H, 3.64; N, 11.89. Found: C, 58.60; H, 3.65; N, 11.92; MS m/z: [M + H]⁺ 472.18.

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### Compound 6g

- **C₂₃H₁₉FN₄OS**: C, 66.01; H, 4.58; N, 13.39. Found: C, 66.03; H, 4.59; N, 13.41; MS m/z: [M + H]⁺ 419.23.

### Compound 6i

- **White powder; mp 180 °C IR (KBr) cm⁻¹: 3094, 1536, 1212. ¹H NMR (DMSO-d₆, 400 MHz): δ 1.55 (s, 3H, ArH), 4.62 (q, J = 7.2 Hz, 1H, CH), 7.23 (dd, J = 8.0 Hz, 1H, ArH), 7.35–7.50 (m, 6H, ArH), 7.61 (dd, J = 8.4 Hz, 1H, ArH), 7.83 (dd, J = 2.0 Hz, 1H, ArH), 8.05 (d, J = 8.4 Hz, 1H, ArH), 10.78 (s, 1H, N=CH), 14.09 (s, 1H, NH) ppm. ¹³C NMR (DMSO-d₆, 101 MHz): δ 19.7, 35.7, 115.6 (d, J = 24.2 Hz), 124.3 (d, J = 3.0 Hz), 127.3 (d, J = 14.1 Hz), 128.3, 128.8, 129.0, 129.1, 129.2 (d, J = 3.0 Hz), 129.5, 130.3, 131.4 (d, J = 4.0 Hz), 135.2, 136.3, 138.2, 143.8 (d, J = 8.1 Hz), 153.8, 155.3, 159.4 (d, J = 24.7 Hz), 162.0 ppm. Anal. Calcd for C₂₃H₂₁F₂N₄O₅S: C, 58.60; H, 3.64; N, 11.89. Found: C, 58.60; H, 3.63; N, 11.92; MS m/z: [M + H]⁺ 472.18.

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### Compound 6h

- **C₂₃H₂₁F₂N₄O₅S**: C, 58.60; H, 3.64; N, 11.89. Found: C, 58.63; H, 3.65; N, 11.92; MS m/z: [M + H]⁺ 471.00.
4.2.2.9. 3-\((1-(2\text{-fluoro-}[1,1']\text{-biphenyl]-4-yl})\text{ethyl})-4-((4\text{-nitrobenzylidene})\text{amino})-1H-1,2,4\text{-triazole-5(4H)}\text{-thione}\) (6i). Dark yellow powder; mp 208 °C. IR (KBr) cm\(^{-1}\): 3098, 1579, 1278; \(^1\text{H} \text{NMR (DMSO-}d_6, 400 \text{MHz):} \delta 1.65 (d, J = 7.2 \text{ Hz}, 3H, CH})_3, 4.59 (q, J = 7.2 \text{ Hz}, 1H, CH)\), 7.23 (dd, J = 8.0 \text{ Hz}, 1.6 \text{ Hz}, 1H, ArH)\), 7.27 (dd, J = 11.6 \text{ Hz}, 1.6 \text{ Hz}, 1H, ArH)\), 7.35–7.48 (m, 6H, ArH)\), 8.09 (d, J = 8.8 \text{ Hz}, 2H, ArH)\), 8.34 (d, J = 8.8 \text{ Hz}, 2H, ArH)\), 10.32 (s, 1H, N=CH)\), 14.10 (s, 1H, NH) ppm; \(^{13}\text{C} \text{NMR (DMSO-}d_6, 101 \text{ MHz):} \delta 19.3, 35.4, 115.2 (d, J = 23.2 \text{ Hz}), 124.0 (d, J = 3.0 \text{ Hz}), 124.3, 126.9 (d, J = 13.1 \text{ Hz}), 127.9, 128.7, 128.8 (d, J = 3.0 \text{ Hz}), 129.7, 131.1 (d, J = 3.0 \text{ Hz}), 134.8, 138.3, 143.3 (d, J = 8.1 \text{ Hz}), 149.5, 153.3, 159.0 (d, J = 247.5 \text{ Hz}), 159.2, 161.8 ppm; Anal. Calcd for C\(_{23}\)H\(_{18}\)FN\(_5\)O\(_2\)S: C, 61.46; H, 4.48; N, 15.58. Found: C, 61.49; H, 4.49; N, 15.61; MS m/z: [M + H]\(^+\) 448.11.

| Table 4. Analgesic Activity by the Acetic Acid Induced Writhing Method |
| treatment | dose mg/kg orally | mean no. of writhes ± SEM | inhibition (%) |
|------------|------------------|-------------------------|----------------|
| control    | 0.5 mL saline    | 57 ± 1.86               | 29 ± 0.951      |
| flurbiprofen| 10 mg/kg        | 20.83 ± 1.249           | 10.83 ± 0.601   |
| 6a         | 10 mg/kg         | 17.17 ± 0.872           | 5.33 ± 0.760    |
| 6b         | 10 mg/kg         | 20.17 ± 1.720           | 6.83 ± 1.351    |
| 6c         | 10 mg/kg         | 20 ± 1.483              | 5.67 ± 0.881    |
| 6d         | 10 mg/kg         | 18.67 ± 1.646           | 5.50 ± 0.992    |
| 6e         | 10 mg/kg         | 18.33 ± 2.108           | 5.67 ± 0.881    |
| 6f         | 10 mg/kg         | 18 ± 1.612              | 5.83 ± 1.612    |
| 6g         | 10 mg/kg         | 18.33 ± 1.429           | 6.17 ± 1.429    |
| 6h         | 10 mg/kg         | 19 ± 2.049              | 6.5 ± 1.176     |
| 6i         | 10 mg/kg         | 24 ± 2.082              | 7.5 ± 0.992     |
| 6j         | 10 mg/kg         | 21.83 ± 1.447           | 6.33 ± 0.666    |
| 6k         | 10 mg/kg         | 21 ± 1.825              | 8.33 ± 0.881    |
| 6l         | 10 mg/kg         | 21.17 ± 2.300           | 6 ± 0.966       |
| 6m         | 10 mg/kg         | 22.5 ± 1.746            | 6.33 ± 0.881    |

Figure 4. Analgesic activity by the hot plate method.

Figure 5. Analgesic activity by the acetic acid induced writhing method.
4.2.2.10. 4-((4-Dimethylamino)benzylidene)amino)-3-(1-(2-fluoro-[1,1'-biphenyl]-4-yl)ethyl)-1H-1,2,4-triazole-5(4H)-thione (6j). Yellow-colored powder; mp 210 °C. IR (KBr) cm^-1: 3133, 1554, 1199; 1H NMR (DMSO-d_6, 400 MHz): δ 1.61 (d, J = 7.2 Hz, 3H, CH_3); 3.02 (s, 6H, N(CH_3)_2); 4.44 (q, J = 7.2 Hz, 1H, CH); 6.77 (d, J = 8.8 Hz, 2H, ArH); 7.15 (dd, J = 8.0 Hz, 1.6 Hz, 1H, ArH); 7.20 (dd, J = 12.0 Hz, 1.2 Hz, 1H, ArH); 7.36–7.48 (m, 6H, ArH); 7.61 (d, J = 9.2 Hz, 2H, ArH); 9.27 (s, 1H, N=CH); 13.84 (s, 1H, NH) ppm; 13C NMR (DMSO-d_6, 101 MHz): δ 19.1, 35.5, 39.7, 111.6, 115.3 (d, J = 23.2 Hz), 118.7, 123.9, 126.8 (d, J = 13.1 Hz), 127.9, 128.7, 128.8 (d, J = 3.0 Hz), 130.4, 130.9 (d, J = 3.0 Hz), 134.9, 143.4 (d, J = 7.1 Hz), 152.7, 152.9, 159.0 (d, J = 246.5 Hz), 167.1, 165.0 ppm; Anal. Calc’d for C_{25}H_{23}FN_4O_2S: C, 64.92; H, 5.01; N, 14.28. Found: C, 64.30; H, 4.38; N, 14.33; MS m/z: [M + H]^+ 393/16.

4.3. X-ray Data Collection and Structure Determination. Crystal data for 6a: C_{25}H_{23}FN_4S, M = 402.48, triclinic, a = 7.4736(4), b = 10.2302(6), c = 13.6343(7) Å, α = 100.3807(7), β = 103.3547(8), γ = 91.5795(8) °, U = 1007.40(9) Å^3, β = 75.2, T = 150(2) K, and space group P1. Data were collected on a Bruker APEX 2 CCD diffractometer using graphite-monochromated Mo Kα radiation, λ = 0.71073 Å. 16217 reflections measured, 6117 unique, and R_{int} = 0.018. The structure was solved by direct methods and refined by full-matrix least squares on F^2.

4.4. Analgesic Activity Methods. 4.4.1. Tail Flick Method. The analgesic activity was determined by the tail immersion method. 30,31 The distal 5 cm portion of tails of Swiss albino mice of either sex weighing between 20 and 40 g were marked and immersed into the water bath maintained at exactly 55 ± 1.0 °C. The reaction time for withdrawal of tails as a reflex action from the water was recorded with and without oral administration of the test compounds 6(a–m) along with standard flurbiprofen (10 mg/kg). The readings for each test compound were recorded for six albino mice at the time intervals of 0.5, 1, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, and 4.5 h, which are tabulated in Table 2. All the results are presented as mean ± SEM, and one-way ANOVA considering P < 0.05 as significant is used to calculate the statistical significance.

4.4.2. Hot Plate Method. The central analgesic effect was measured by the hot plate method originally developed by MacDonald and co-workers. 32 Animals (20–40 g) were divided into groups of six, and each Swiss albino mouse was placed individually on the surface of the hot plate maintained at 52 ± 1 °C until it licked its forepaw or jumped, and the time was noted cautiously. The cut off time in the absence of response was set to 15 s to prevent tissue damage. The first group served as the positive control with no oral administration; the second group of animals were given a dose of the standard flurbiprofen (10 mg/kg) while other groups were administered with the test compounds 6(a–m). Readings were recorded after each 30 min interval till 4.5 h and are given in Table 3. The analgesic activity for each mouse was calculated as a percentage of the maximum possible effect (MPE %), where MPE % = ((test latency − control latency)/(cut-off point − control latency)) × 100.

Statistical Analysis: The results are presented as mean ± SEM, one-way ANOVA considering P < 0.05 as significant is used to calculate the statistical significance.

4.4.3. Acetic Acid Induced Writhing Method. Swiss albino mice divided into groups of six, weighing between 20 and 40 g, were used for the evaluation of analgesic activity by acetic acid induced writhing method. 33,34 The animals of group I, serving as control, were treated with 10 mL/kg of normal saline administered orally, group II was treated with 10 mg/kg of flurbiprofen as the standard drug, while the rest of the groups...
were treated with 10 mg/kg of the test compounds. After 30 min, each mouse was administered with acetic acid (0.6% in normal saline) and was immediately shifted into a visible glass chamber for counting of induced writhes during the next 30 min. Percent analgesic activity of each group was determined as

\[
\text{percent inhibition} = \frac{(X - Y)}{X} \times 100
\]

where \(X\) = average count of writhes for the control group and \(Y\) = average count of writhes for the group administered with test compound.

The results of acetic acid induced writhing are presented in Table 4.

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