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RESEARCH ARTICLE

Novel Para-Fluorophenyl Derivatives: Synthesis, Characterization, and Antipsychotic Screening

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ABSTRACT

Para-fluorophenyl derivatives are of critical importance in drug development owing to their enhanced pharmacokinetic and metabolic characteristics. This research aims to synthesize and determine the characteristics of new para-fluorophenyl derivatives via acid-amine coupling and Suzuki cross-coupling reactions. The structures of these compounds and their possible. P1 and P2 were synthesized through acid-amine coupling with p-fluoro benzoic acid and lysine and then subjected to BOC protection, deprotection, and hydrolysis. The Suzuki cross-coupling reaction was used to prepare P3 using (4-cyanophenyl) boronic acid. Further derivatives (P4-P9) were prepared via benzoyl, urea, and sulfonyl chloride reactions. The structures were established using melting point analysis, TLC, IR, NMR, and mass spectrometry. Antipsychotic activity in mice was determined using the Elevated Plus Maze method, and statistical analysis was performed using one-way ANOVA and Tukey's test. The synthesized compounds yielded 68-84%, and the spectral data verified their structures. Pharmacological assessment revealed that P1, P3, P8, and P9 were significantly active ($P<0.001$) as antipsychotics. P1 displayed significant open-arm activity ($P<0.05$), whereas P3 and P8 exhibited highly significant closed-arm effects ($P<0.01$). This study introduces new para-fluorophenyl derivatives with improved antipsychotic activities. This new synthetic approach effectively synthesizes structurally varied fluorinated compounds, providing potential candidates for future drug development.

Keywords: Para-Fluoro Phenyl Derivatives; Antipsychotic Activity; Suzuki Cross-Coupling

INTRODUCTION

The synthesis and characterization of novel analogs of para-fluorophenyl derivatives have received significant attention in medicinal chemistry because of their versatile pharmacological uses. Fluorine, a special and highly electronegative atom, plays a significant role in influencing the physicochemical and biological properties of organic compounds. Its inclusion in drug molecules can have a dramatic impact on parameters such as lipophilicity, metabolic stability, receptor-binding affinity, and bioavailability, rendering fluorinated compounds highly useful in drug discovery and development.[1] The antipsychotic activity of fluorinated compounds is an area of interest. Most clinically interesting antipsychotic medications such as haloperidol and fluoxetine have fluorine functionalities, underscoring the importance of fluorinated platforms in neuropsychiatric medicines. The incorporation of a fluorine atom within a molecular scaffold has been shown to optimize the blood-brain barrier permeability and facilitate drug-receptor interactions, both of which are essential for CNS medicines.[2]

The key aims of the current research are the synthesis, purification, and thorough structural evaluation of new para-fluorophenyl analogs. This has been achieved using various analytical methods including Liquid Chromatography-Mass Spectrometry (LC-MS), High-Performance Liquid Chromatography (HPLC), Proton Nuclear Magnetic Resonance (^1H-NMR), and Infrared (IR) spectroscopy. These analytical methods will assist in exact structural elucidation and purity testing of the produced compounds. In addition, this study aimed to assess the potential antipsychotic activity of these derivatives using relevant biological tests and to measure their effectiveness as prospective candidates for CNS drug discovery. This multidisciplinary research strategy is consistent with current medicinal chemistry trends in

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which the rational design of fluorinated compounds is complemented by detailed physicochemical characterization and biological evaluation. Utilizing advanced synthetic routes, including multicomponent processes (e.g., the Ugi reaction), scientists can cost-effectively synthesize structurally varied fluorinated derivatives with druglike pharmacology.[3]

Surprisingly, although fluorinated compounds are uncommon in nature, their synthetic equivalents have been proven to have exceptional pharmacological value. The judicious introduction of fluorine atoms into drug molecules can provide a number of benefits, such as improved metabolic stability, enhanced lipophilicity and membrane permeability, and streamlined drug-receptor interactions. Metabolic degradation by cytochrome P450 enzymes is frequently diminished by fluorine substitution, leading to the extension of drug half-life and increased oral bioavailability. Fluorinated drugs tend to display enhanced penetration across lipid membranes, which is advantageous for therapies directed towards the CNS. In addition, the ability of fluorine to influence electronic effects can improve its binding affinity to desired protein targets, resulting in higher potency and selectivity.[1] Additionally, contemporary synthetic methodologies, such as green chemistry techniques and catalyst-facilitated fluorination methodologies, have enabled the efficient production of fluorinated derivatives with minimal environmental impact. The use of these approaches may enable the identification of new antipsychotic drugs with improved therapeutic profiles.[4,5]

MATERIALS AND METHODS

Coupling of compounds P-1 and P-2 was performed using a two-step procedure. First, methyl 2-amino-6-((tert-butoxycarbonyl)amino)hexanoate and TEA were stirred in the MDC for 15 min. p-Fluoro benzoic acid was then added along with T3P at 0°C and the reaction mixture was stirred for five hours at room temperature under nitrogen. The reaction mixture was extracted using ethyl acetate, concentrated, and dried. To prepare P-1, the product from the first step was treated with a combination of TFA and MDC and stirred for four hours. The obtained mixture was extracted with ethyl acetate, concentrated, and dried. To prepare P-2, methyl 2-amino-6-((tert-butoxycarbonyl)amino)-2-(4-Fluoro benzamido)hexanoate was stirred with lithium hydroxide in THF and water (1:1) for four hours. The reaction mixture was concentrated, extracted with ethyl acetate, and then dried.

The synthesis of P-3 was a three-step process. In the first step, p-fluoro iodobenzene, 4-cyanophenyl boronic acid, sodium carbonate, and tetrakis were stirred overnight in 1, 2-dioxane and water under nitrogen pressure at 85°C. The reaction mixture was extracted with ethyl acetate, concentrated, and dried. In the second step, the obtained product was stirred with concentrated HCl and 1,4-dioxane at 100°C for three hours. The reaction mixture was dried, concentrated, and extracted using ethyl acetate. p-Fluoro aniline and TEA were stirred in the MDC for 15 min in the last step, after which the acid derivative and T3P were added. The reaction mixture was stirred for five hours under nitrogen atmosphere, extracted in ethyl acetate, concentrated, and dried.

For P-4 to P-9 synthesis, p-fluoro aniline, TEA, and MDC were mixed at 0°C for 15 min before the respective reagents were added. For P-4, dropwise p-Fluoro benzoyl chloride was added, and the reaction mixture was stirred for four hours, extracted with MDC, washed, concentrated, and dried. P-5 was prepared using the same method but with benzoyl chloride. The synthesis of P-6 included the dropwise addition of p-fluorophenyl isocyanate, while that of P-7 employed phenyl isocyanate. P-8 was synthesized by dropwise addition of p-fluorobenzene sulfonyl chloride, and for P-9, 4-(trifluoromethyl) benzene sulfonyl chloride was employed. All the reaction mixtures were stirred for four hours, extracted, washed, concentrated, and dried.

The synthesized compounds were identified by melting point determination, thin-layer chromatography (TLC), infrared (IR) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry. The melting points were obtained using the Thiel's tube method. TLC was performed on pre-coated silica plates using suitable solvent systems, and the Rf values were measured under UV light. IR spectroscopy was obtained by a SHIMADZU FTIR 8400S spectrometer, whereas NMR spectra were measured by a Bruker spectrospin-400 NMR spectrophotometer in $CDCl_3$ and DMSO solvents. Mass spectrometry analysis was performed using an electron spray mass spectrometer to validate molecular weights and structural integrity.

The synthesized compounds were also tested for antipsychotic activity using the elevated plus-maze model. Mice were categorized into 11 groups: a control, a standard drug group treated with haloperidol, and nine test groups treated with varying synthesized derivatives. All mice were introduced separately to the maze, and entries into the open and enclosed arms, as well as the time spent in each of the arms, were counted over a period of five minutes. Observations between groups were compared after 30 minutes of administration of the compound. Statistical tests were conducted using one-way ANOVA and Tukey's test, with significance at different p values. This study sheds valuable light on the antipsychotic activities of the synthesized compounds.

RESULTS

p-Fluoro phenyl derivatives were successfully synthesized by employing various synthetic protocols. p-Fluoro benzoic acid and the amino acid lysine, through acid-amine coupling with BOC protection and subsequent deprotection and hydrolysis, produced compounds structurally similar to

haloperidol (P1, P2). Another route, the Suzuki reaction with (4-cyanophenyl) boronic acid, produced P3. Several derivatives, such as amides, ureas, and sulphonamides, have also been prepared by fluoro substitution at the para position (Table 1).

Table 1: Data on the various derivatives synthesized

Compound code	Molecular formula	Molecular weight	Melting point (°C)	Yield (%)	Rf Value
P1	C14H19FN2O3	282.31	Liquid state	78	0.6
P2	C18H25FN2O5	368.40	Not melted up to 300 °C	71	0.16
P3	C19H13F2NO	309.20	238.1-240.2	73	0.32
P4	C13H9F2NO	233.21	182- 185.6	79	0.67
P5	C13H10FNO	215.22	183.1-184.9	80	0.61
P6	C13H10F2N2O	248.23	237	84	0.36
P7	C13H11FN2O	230.24	254.2-255	82	0.34
P8	C12H9F2NO2S	269.27	90-103.1	79	0.87
P9	C13H9F4NO2S	319.27	133.6-135.9	68	0.81

The synthesized compounds were identified using various analytical methods. Melting points were found with the help of Thiel's melting point tube (capillary method). Thin Layer Chromatography (TLC) was conducted with a mobile phase of petroleum ether and ethyl acetate in appropriate proportions. Infrared (IR) spectroscopy was performed using KBr pellets, and Nuclear Magnetic Resonance (NMR) spectroscopy was performed on a 400 Spectrospin at Syngene International Ltd., Bangalore, using solvents such as CDCl3 and DMSO. Mass spectroscopy was performed using Electron Spray Ionization (ESI) at the same center. The spectral data obtained validated the structures of the synthesized derivatives.

Pharmacological screening was performed to assess the antipsychotic activity of the synthesized compounds with respect to the standard drug haloperidol. The elevated plus maze method was used to calculate the time spent in the open and closed arms and the number of entries into the open arm. The findings proved that the synthesized derivatives, especially P1, P2, P3, P6, P7, P8, and P9, had statistically significant antipsychotic activities compared with the control group ($P<0.001$). In particular, P1 showed significant differences in the open arm compared to the standard ($P<0.05$), whereas P3 showed highly significant activity in the closed arm ($P<0.01$). In addition, P8 and P9 exhibited considerable activity in the closed arm compared to the control ($P<0.05$) (Table 2).

Table 2: Time spent in open arm and closed arm

Treatment	Time spent in open arm Mean ± S.E.M	Time spent in closed arm Mean ± S.E.M
Control	3.34±0.25	0±0.00
Standard	0±0.00***	4.57±0.01***
P1	0.32±0.207***a	3.57±0.3***
P2	0.21±0.10***	3.59±0.4***
P3	0.13±0.066***	2.61±0.5***aa
P4	0±0.00***	0±0.00aaa
P5	0±0.00***	0±0.00aaa
P6	0.29±0.23***	3.22±0.31***
P7	0.15±0.07***	3.38±0.266***
P8	0.38±0.07***	2.78±0.54***a
P9	0.5±0.07***	2.70±0.40***a

***=Highly significant

These findings, analyzed using one-way ANOVA followed by Tukey's test for multiple comparisons, confirmed the potential of the synthesized derivatives as promising antipsychotic agents (Figures 1 and 2).

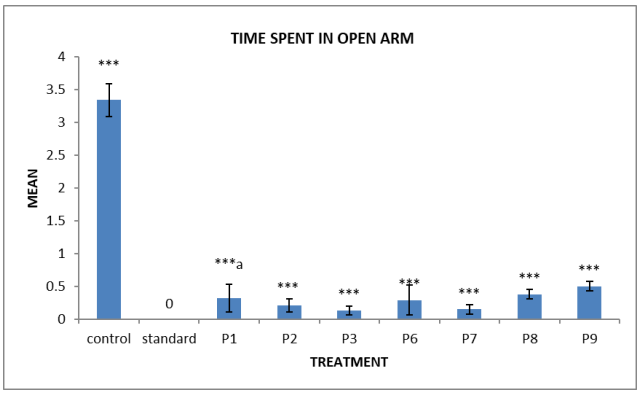

Fig. 1: Time spent in open arm

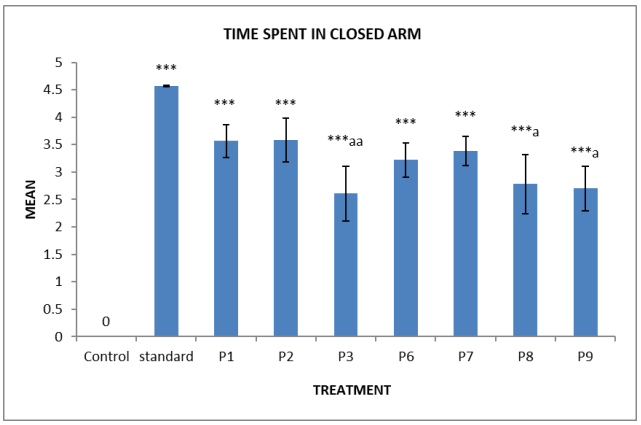

Fig. 2: Time spent in closed arm

DISCUSSION

The synthesis of para-fluorophenyl derivatives using diverse synthetic routes is compatible with the current trends in organic chemistry, especially in pharmaceutically relevant compound design and development. The relevance of such derivatives relies on their possible therapeutic use, because fluorine substitution of aromatic molecules tends to render the resulting compounds more metabolically stable, bioavailable, and drug-like in drug discovery.

A particularly interesting strategy used in this synthesis is acid-amine coupling, which has been effectively utilized to produce haloperidol-analogous compounds (P1, P2). This strategy is a perfect example of the utility of amide bond formation in drug discovery, thus enabling the design of new antipsychotic lead candidates. The versatility of this strategy has been adequately demonstrated in the literature[6], showing its potential for the production of structurally diverse and pharmacologically relevant compounds.

Another important response that was applied in this work is the Suzuki-Miyaura cross-coupling reaction, which was utilized to prepare compound P3 with (4-cyanophenyl) boronic acid. This conversion underlines the extensive utility of palladium-catalyzed cross-coupling in the construction of aryl-substituted frameworks, which are the central components of many bioactive compounds. The tolerance and efficiency of the reaction in creating intricate aromatic frameworks have been amply reported in the literature[7–9], highlighting its sustained utility in contemporary synthetic protocols.

In addition to particular examples, the synthesis of other para-fluoro derivatives such as amides, ureas, and sulphonamides also highlights the prospect of broadening the chemical space of bioactive compounds. This method allows the creation of a large library of fluorinated compounds with potentially diverse biological activities. Appukkuttan et al.[10] also reported a similar approach, in which electron-rich 2-[4,5-dimethoxy-2-(hetero)arylphenyl]ethylamines were prepared through the Suzuki-Miyaura reaction, demonstrating the efficiency of such methods in medicinal chemistry.

The presence of fluorine atoms in these molecules is especially significant because the broad impact of fluorine on the physicochemical and pharmacokinetic properties of organic compounds is well documented. Fluorination increases lipophilicity, tunes electronic effects, and enhances metabolic stability, thereby substantially affecting biological activity and therapeutic value.[11] Therefore, the strategic incorporation of fluorine into synthetic candidate drugs continues to be a major thrust in pharmaceutical science, reaffirming the tenacity of these synthetic methods for current drug discovery.

CONCLUSION

The synthesis of para-fluorophenyl derivatives emphasizes the efficiency of known synthetic protocols for the production of promising bioactive molecules. Employing acid-amine coupling and Suzuki cross-coupling facilitated the synthesis of diverse molecules along with haloperidol-like architectures (P1, P2) and aryl derivatives (P3), in addition to amide, urea, and sulfonyl-containing compounds. The synthesized molecules, as ascertained by spectral studies (MP, TLC, IR, NMR, MASS, and HPLC), were found to have yields between 68-84%. Biological screening indicated that a number of derivatives, especially those with p-fluorophenyl moieties comprising lysine (P1), phenyl boronic acid (P3), and sulfonyl moieties (P8, P9), showed significant antipsychotic activity, similar to that of the control drug haloperidol.

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