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Short Note

2-{[4-(4-Bromophenyl)piperazin-1-yl)]methyl}-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione

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Abstract: The novel compound 2-{[4-(4-bromophenyl)piperazin-1-yl)]methyl}-4-(3-chlorophenyl-5-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione is obtained in good yield via a three-step protocol. The product's structure is assigned by HRMS, IR, ^{1}H and ^{13}C NMR experiments.

Keywords: 1,2,4-triazole; mannich base; NMR analysis

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1. Introduction

Piperazine is a common structural motif found in agrochemicals and pharmaceuticals, in part due to its ability to positively modulate the pharmacokinetic properties of a drug substance. The incorporation of this heterocycle into biologically active compounds can be accomplished through a Mannich reaction [1]. Piperazine can be found in biologically active compounds for a variety of disease states, such as antihistamines, antiparasitic, antifungal, antibacterial, antiviral, antipsychotic, antidepressant, anti-inflammatory, anticoagulant, antitumor, and antidiabetic drugs [2–26]. Additionally, the piperazine ring is a component in potential treatments for Parkinson's and Alzheimer's disease [27–31], and known antibiotic drugs Ciprofloxacin and Ofloxacin. Moreover, they are also used as psychoactive substances used illegally for recreational purposes [32,33].

We previously described some new derivatives of 1,2,4-triazole with piperazine moiety, some of which exhibited good antibacterial activity [34].

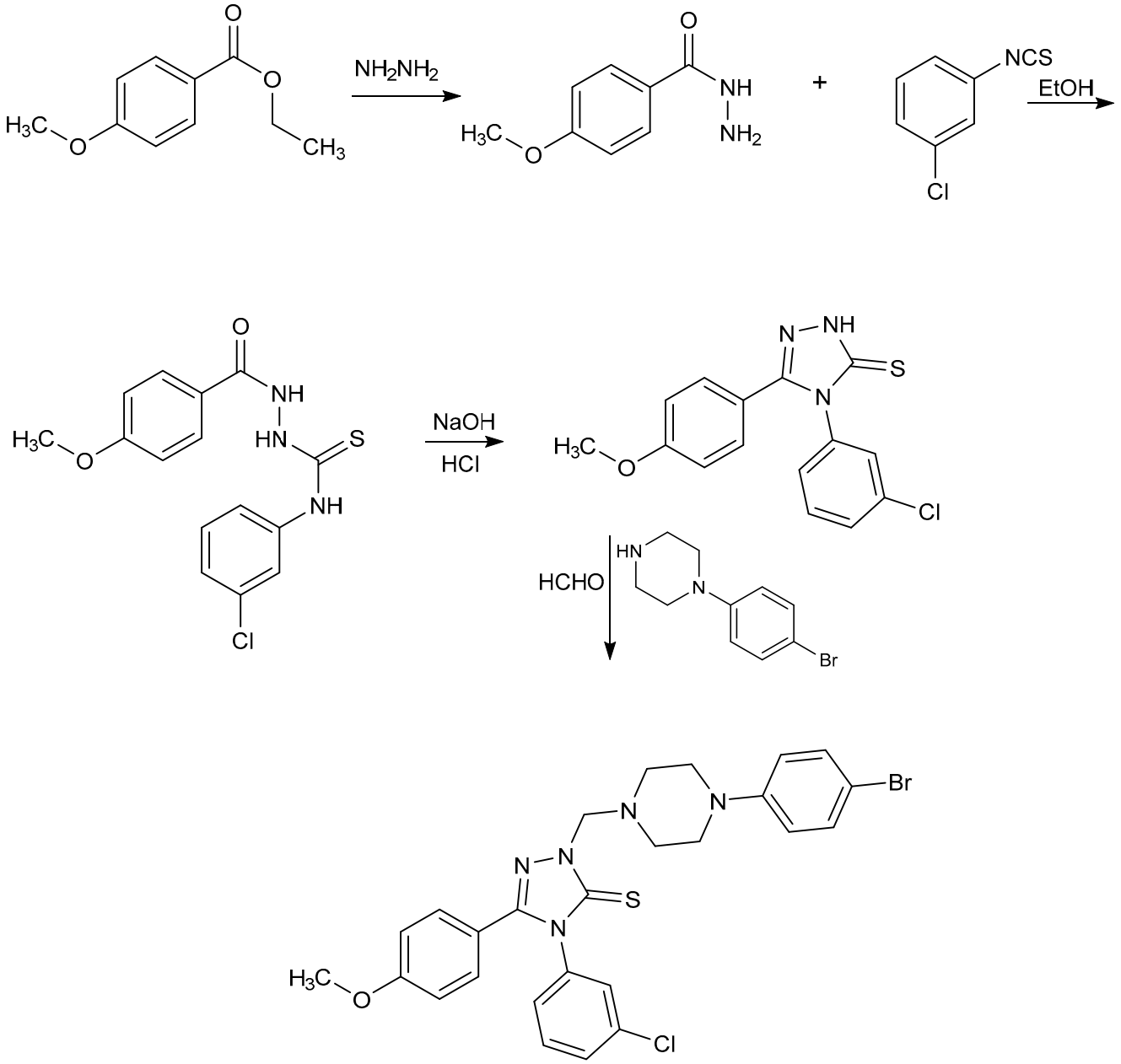
Herein, we report on the synthesis and characterization of a novel Mannich derivative with promising antibacterial activity.

2. Results and Discussion

The title compound 2-{[4-(4-bromophenyl)piperazin-1-yl)]methyl}-4-(3-chlorophenyl-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione is obtained via a four-step protocol, shown in Scheme 1. The 1,2,4-triazole derivative is prepared in the very simple and efficient procedure described previously [35]. The reaction with amine was carried out in 95% ethanol at room temperature for 24 h. The progress of the reaction was checked by TLC chromatography using the mixture $CHCl_3$: C_2H_5OH (10:1 *v*/*v*) as eluent.

The structure of the new Mannich base is assigned by HRMS, IR, ^{1}H, and ^{13}C NMR spectra (see Supplementary Materials). The ^{1}H spectrum in DMSO-d_6 shows characteristic signals for the protons of piperazine at 2.96 and 3.16 ppm, respectively, protons of the methoxy group as a singlet at 3.75 ppm, the signal of the CH_2 group at 5.23 as a singlet, and aromatic protons in the range 6.92–7.67. There is a lack of signal characteristics for the proton NH group present in the spectrum of the initial compound. In the ^{13}C NMR spectra, carbons signals were observed at expected values of chemical shift. The six aliphatic carbon were observed as four signals at 48.46, 50.14, 55.81, and 69.21 ppm. The IR spectra of

products show a characteristic band for CH aliphatic and aromatic stretch at 2883 cm^{-1}, 2831 $cm^{-1,}$ and 3040 cm^{-1}, respectively.



Scheme 1. Synthesis of 2-{[4-(4-bromophenyl)piperazin-1-yl)]methyl}-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione.

3. Materials and Methods

3.1. General

All reagents were purchased from Merck (Darmstadt, Germany) and were used without any further purification. Solvents (ethanol, dry ethanol, diethyl ether, chloroform) were used as purchased (POCH Gliwice, Poland). Merck silica gel (TLC-cards with fluorescent indicator 254 nm) was used for TLC chromatography. The NMR spectra were recorded on a Bruker Avance 600 spectrometer (Rheinstetten, Germany) in DMSO-d_6; the chemical shifts were quoted in ppm in δ-values and the coupling constants were calculated in Hz. The spectra were processed with the Topspin 3.6.2 program. The IR spectra were measured on a Spectrometer FT-IR Nicolett 8700 (Thermo Scientific, Waltham, MA, USA).

The chromatographic measurements were performed using LC/MS system consisting of UHPLC chromatograph (UltiMate 3000, Dionex, Sunnyvale, CA, USA) connect whit the linear trap quadrupole-Orbitrap mass spectrometer (LTQ-Orbitrap Velos from Thermo Fisher Scientific, San Jose, CA, USA) equipped with ESI source. In all analyses a Gemini C18 column (4.6 × 100 mm, 3 µm) (Phenomenex, Torrance, CA, USA) was used for chromatographic separation.

3.2. Synthesis of 2-{[4-(4-Bromophenyl)piperazin-1-yl]methyl}-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione

3.2.1. Synthesis of 4-Methoxybenzhydrazide [35]

Ethyl 4-methoxybenzoate (1 mmol, 0.18 g) was dissolved in 5 mL of 96% ethanol and hydrazine hydrate (100%) (2 mL) was added. The mixture was refluxed for 3 h. After the completion of the reaction by TLC (toluene:ethyl acetate = 7:3 *v*/*v*), the solution was cooled and the precipitate was filtered off and dried. 4-Methoxybenzhydrazide was obtained with 85% yield (0.14 g).

3.2.2. Synthesis of 4-(3-Chlorophenyl)-1-(4-methoxyphenyl)thiosemicarbazide [35]

In the next step, hydrazide (1 mmol, 0.17 g) and 3-chlorophenyl isothiocyanate (1 mmol, 0.13 mL) was refluxed for 2 h in anhydrous ethanol (5 mL). Then, the solution was cooled to room temperature. The solid product was filtered off, washed with hot water and diethyl ether, dried, and crystallized from 96% ethanol.

3.2.3. Synthesis of 4-(3-Chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione [35]

The obtained thiosemicarbazide derivative (0.31 g, yield 90%) was refluxed with 2% NaOH solution for 4 h. Next, the solution was cooled and acidified (6N HCl). The solid product was filtered and crystallized from 96% ethanol. 4-(3-Chlorophenyl)-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione was obtained as a white solid to yield 0.22 g (70%). M.p. 261–262 °C.

3.2.4. Synthesis of 2-{[4-(4-Bromophenyl)piperazin-1-yl]methyl}-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione

A total of 1 mmol (0.32 g) of the 4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione was dissolved in 10 mL anhydrous ethanol and then 4-(4-bromo phenyl)piperazine (1 mmol, 0.24 g) and a formaldehyde solution (aq. 37 %, 5 drops) were added. The mixture was stirred at room temperature for 1 h. The appearance of the product was observed. However, the complete reaction of the substrates took place after 24 h at room temperature. The progress of the reaction was checked by TLC chromatography (eluent chloroform:96% ethanol, 10:1 *v*/*v*). The precipitate was filtered off, dried, and crystallized from 96 % ethanol.

Yield: 81 %, 0.46 g. White crystals, m.p.: 226–227 °C. ^{1}H NMR (600 MHz (d_6)DMSO): 2.95–2.97 (m, 4H, 2CH_2 piperazine,), 3.15–3.17 (m, 4H, 2CH_2 piperazine), 3.75 (s, 3H, CH_3) 5.25 (s, 2H, N-CH_2,), 6.90 (d, 2H, ArH, *J* = 9.1 Hz), 6.95 (d, 2H, ArH, *J* = 8.9 Hz), 7.29 (d, 2H, ArH, *J* = 8.9 Hz), 7.34 (d, 2H, ArH, *J* = 9.1 Hz), 7.37–7.38 (m, 1H, ArH), 7.53 (t, 1H, ArH, *J* = 8.0 Hz), 7.58–7.60 (m, 1H, ArH), 7.67 (t, 1H, ArH, *J* = 2.0 Hz). ^{13}C NMR (600 MHz, (d_6)DMSO): 48.46, 50.14, 55.81, 69.21, 110.56, 114.60, 117.73, 117.96, 128.31, 129.61, 130.16, 130,55, 131.39, 131.94, 133.77, 136.96, 149.36, 150.69, 161.33, 169.72. IR (KBr, cm^{-1}): 3040 ($CH_{arom.}$), 2883, 2831 ($CH_{aliph.}$), 1326 (C=S). HRMS (ESI), *m*/*z*: calcd for $C_{26}H_{25}BrClN_5OS$. Theoretical mass $[M + H]^+$ 570.07300, Experimental mass $[M + H]^+$ 570.07309.

4. Conclusions

2-{[4-(4-bromophenyl)piperazin-1-yl]methyl}-4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione is obtained in good yield by aminomethylation reac-

tion of 4-(3-chlorophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione with 4-(4-bromophenyl)piperazine and formaldehyde. The product is purified by crystallization from 96% ethanol and characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS spectra.

Supplementary Materials: The following are available online: ^{1}H, ^{13}C NMR, and IR spectra.

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References

1. Gul, H.I.; Tugrak, M.; Gul, M.; Mazlumoglu, S.; Sakagami, H.; Gulcin, I.; Supuran, T. New phenolic Mannich bases with piperazines and their bioactivities. *Bioorg. Chem.* **2019**, *90*, 103057. [CrossRef]
2. Hafeez, F.; Zahoor, A.F.; Rasul, A.; Ahmad, S.; Mansha, A. Synthesis and anticancer evaluation of 2-oxo-2-(arylamino)-ethyl 4-phenylpiperazine-1-carbodithioates. *Pak. J. Pharm. Sci.* **2021**, *34*, 353–357. [PubMed]
3. Al-Soud, Y.A.; Alhelal, K.A.S.; Saeed, B.A.; Abu-Qatouseh, L.; Al-Suod, H.H.; Al-Ahmad, H.; Al-Masoudi, N.A.; Al-Qawasmeh, R.A. Synthesis, anticancer activity and molecular docking studies of new 4-nitroimidazole derivatives. *Arkivoc* **2021**, *8*, 296–309. [CrossRef]
4. Zárate, A.M.; Espinosa-Bustos, C.; Guerrero, S.; Fierro, A.; Oyarzún-Ampuero, F.; Quest, A.F.G.; Di Marcotullio, L.; Loricchio, E.; Caimano, M.; Calcaterra, A.; et al. A New Smoothened Antagonist Bearing the Purine Scaffold Shows Antitumour Activity In Vitro and In Vivo. *Int. J. Mol. Sci.* **2021**, *22*, 8372. [CrossRef] [PubMed]
5. Abba, C.; Puram, N.; Betala, S. Synthesis of Novel Amide Functionalized Pyrido[2,3-d]pyrimidine Derivatives and their Anticancer Activity. *Asian J. Chem.* **2021**, *33*, 1579–1584. [CrossRef]
6. Alagöz, M.A.; Özdemir, Z.; Uysal, M.; Carradori, S.; Gallorini, M.; Ricci, A.; Zara, S.; Mathew, B. Synthesis, Cytotoxicity and Anti-Proliferative Activity against AGS Cells of New 3(2H)-Pyridazinone Derivatives Endowed with a Piperazinyl Linker. *Pharmaceuticals* **2021**, *14*, 183. [CrossRef]
7. Kaczor, A.; Szemerédi, N.; Kucwaj-Brysz, K.; Dąbrowska, M.; Starek, M.; Latacz, G.; Spengler, G.; Handzlik, J. Computer-Aided Search for 5-Arylideneimidazolone Anticancer Agents Able to Overcome ABCB1-Based Multidrug Resistance. *ChemMedChem* **2021**, *16*, 2386–2401. [CrossRef]
8. Liu, X.; Wang, Y.; Wang, X.; Zhang, Z. Synthesis, in vitro cytotoxicity and biological evaluation of twenty novel 1,3-benzenedisulfonyl piperazines as antiplatelet agents. *Bioorg. Med. Chem.* **2021**, *46*, 116390. [CrossRef]
9. Sowmithri, S.; Kumar, J.V.S.; Mahesh, P.; Krishnamohan, T. Design and Synthesis of Novel Piperazine (2-Chloroethyl)-1-nitrosourea Analogues as Anticancer Agents. *Asian J. Chem.* **2022**, *34*, 591–596. [CrossRef]
10. Baker, J.R.; Russel, C.C.; Gilbert, J.; McCluskey, A.; Sakoff, J.A. Amino alcohol acrylonitriles as broad spectrum and tumour selective cytotoxic agents. *RSC Med. Chem.* **2021**, *12*, 929–942. [CrossRef]
11. Severin, A.O.; Pilyo, S.G.; Potikha, L.M.; Brovarets, V.S. Synthesis and Antitumor Activity of 5-Phenyl-1,3-thiazole-4-sulfonamide Derivatives. *Russ. J. Gen. Chem.* **2022**, *92*, 174–184. [CrossRef]
12. Elgawish, M.S.; Nafie, M.S.; Yassen, A.S.A.; Yamada, K.; Ghareb, N. The design and synthesis of potent benzimidazole derivatives via scaffold hybridization and evaluating their antiproliferative and proapoptotic activity against breast and lung cancer cell lines. *New J. Chem.* **2022**, *46*, 4239. [CrossRef]
13. Patel, S.; Globisch, C.; Pulugu, P.; Kumar, P.; Jain, A.; Shard, A. Novel imidazopyrimidines-based molecules induce tetramerization of tumor pyruvate kinase M2 and exhibit potent antiproliferative profile. *Eur. J. Pharm. Sci.* **2022**, *170*, 106112. [CrossRef]
14. Song, J.; Liu, Y.; Yuan, X.Y.; Liu, W.B.; Li, Y.R.; Yu, G.X.; Tian, X.Y.; Zhang, Y.B.; Fu, X.J.; Zhang, S.Y. Discovery of 1,2,4-triazine dithiocarbamate derivatives as NEDDylation agonists to inhibit gastric cancers. *Eur. J. Med. Chem.* **2021**, *225*, 113801. [CrossRef]
15. Rzycka-Korzec, R.; Malarz, K.; Gawecki, R.; Mrozek-Wilczkiewicz, A.; Małecki, J.G.; Schab-Balcerzak, E.; Korzec, M.; Polanski, J. Effect of the complex-formation ability of thiosemicarbazones containing (aza)benzene or 3-nitro-1,8-naphthalimide unit towards Cu(II) and Fe(III) ions on their anticancer activity. *J. Photochem. Photobiol. A* **2021**, *415*, 113314. [CrossRef]
16. Silalai, P.; Pruksakorn, D.; Chairoungdua, A.; Suksen, K.; Saeeng, R. Synthesis of propargylamine mycophenolate analogues and their selective cytotoxic activity towards neuroblastoma SH-SY5Y cell line. *Bioorg. Med. Chem. Lett.* **2021**, *45*, 128135. [CrossRef]
17. Desai, N.C.; Rupala, Y.M.; Khasiya, A.G.; Shah, K.N.; Pandit, U.P.; Khedkar, V.M. Synthesis, biological evaluation, and molecular docking study of thiophene-, piperazine-, and thiazolidinone-based hybrids as potential antimicrobial agents. *J. Heterocyclic. Chem.* **2022**, *59*, 75–87. [CrossRef]

18. Baker, J.R.; Cossar, P.J.; Blaskovich, M.A.T.; Elliott, A.G.; Zuegg, J.; Cooper, M.A.; Lewis, P.J.; McCluskey, A. Amino Alcohols as Potential Antibiotic and Antifungal Leads. *Molecules* **2022**, *27*, 2050. [CrossRef]
19. Foks, H.; Janowiec, M.; Zwolska, Z.; Augustynowicz-Kopeć, E. Synthesis and Tuberculostatic Activity of Some 2-Piperazinmethylene Derivatives 1,2,4-Triazole-3-Thiones. *Phosphorus Sulfer Silicon* **2005**, *180*, 537–543. [CrossRef]
20. Sutherland, H.S.; Lu, G.; Tong, A.S.T.; Conole, D.; Franzblau, S.G.; Upton, A.M.; Lotlikar, M.U.; Cooper, C.B.; Palmer, B.D.; Choi, P.J.; et al. Synthesis and structure-activity relationships for a new class of tetrahydronaphthalene amide inhibitors of Mycobacterium tuberculosis. *Eur. J. Chem.* **2022**, *229*, 114059. [CrossRef]
21. Patel, A.B.; Rohit, J.V. Development of 1,3,4-Thiadiazole and Piperazine Fused Hybrid Quinazoline Derivatives as Dynamic Antimycobacterial Agents. *Polycycl. Aromat. Compd.* **2022**, *42*, 5991–6002. [CrossRef]
22. Varpe, B.D.; Jadhav, S.B. Schiff Base Conjugate of 5-Fluoroisatin with Thiophene-2-Ethylamine and its Mannich Bases: Synthesis, Molecular Docking, and Evaluation of in vitro Anti-inflammatory and Anti-tubercular Activity. *Int. J. Pharm. Investig.* **2021**, *11*, 189–194. [CrossRef]
23. Gharbi, C.; Toumi, B.; Soudani, S.; Lefebvre, F.; Kaminsky, W.; Jelsch, C.; Nasr, C.B.; Khedhiri, L. Synthesis, structural characterization, antibacterial activity, DFT computational studies and thermal analysis of two new thiocyanate compounds based on 1-phenylpiperazine. *J. Mol. Struct.* **2022**, *1257*, 132620. [CrossRef]
24. Plescia, C.B.; Lindstrom, A.R.; Quintero, M.V.; Keiser, P.; Anantpadma, M.; Davey, R.; Stahelin, R.V.; Davisson, V.J. Evaluation of Phenol-Substituted Diphyllin Derivatives as Selective Antagonists for Ebola Virus Entry. *ACS Infect. Dis.* **2022**, *8*, 942–957. [CrossRef]
25. Mishra, S.; Parmar, N.; Chandrakar, P.; Sharma, C.P.; Parveen, S.; Vats, R.P.; Seth, A.; Goel, A.; Kar, S. Design, synthesis, in vitro and in vivo biological evaluation of pyranone-piperazine analogs as potent antileishmanial agents. *Eur. J. Med. Chem.* **2021**, *221*, 113516. [CrossRef]
26. Kucwaj-Brysz, K.; Dela, A.; Podlewska, S.; Bednarski, M.; Siwek, A.; Satała, G.; Czarnota, K.; Handzlik, J.; Kiec-Kononowicz, K. The Structural Determinants for α1-Adrenergic/ Serotonin Receptors Activity aong PhenylpiperazineHydantoin Derivatives. *Molecules* **2021**, *26*, 7025. [CrossRef]
27. Ji, L.; Fang, Y.; Tang, J.; Liu, C.; Huang, C.; Hu, Q.; Li, Q.; Chen, Z. Synthesis and biological evaluation of 18F-labelled dopamine D3 receptor selective ligands. *Bioorg. Med. Chem.* **2022**, *62*, 128630. [CrossRef]
28. Lee, B.; Taylor, M.; Griffin, S.A.; McInnis, T.; Sumien, N.; Mach, R.H.; Luedtke, R.R. Evaluation of Substituted N-Phenylpiperazine Analogs as D3 vs. D2 Dopamine Receptor Subtype Selective Ligands. *Molecules* **2021**, *26*, 3182. [CrossRef]
29. Waly, O.M.; Saad, K.M.; El-Subbagh, H.I.; Bayomi, S.M.; Ghaly, M.A. Synthesis, biological evaluation, and molecular modeling simulations of new heterocyclic hybrids as multi-targeted anti-Alzheimer's agents. *Eur. J. Med. Chem.* **2022**, *231*, 114152. [CrossRef]
30. Mohammadi-Khanaposthani, M.; Nori, M.; Valizadeh, Y.; Javanshir, S.; Dastyafteh, N.; Moaazam, A.; Hosseini, S.; Larijani, B.; Adibi, H.; Biglar, M.; et al. New 4-phenylpiperazine-carbodithioate-N-phenylacetamide hybrids: Synthesis, in vitro and in silico evaluations against cholinesterase and α-glucosidase enzymes. *Arch. Pharm.* **2022**, *355*, 2100313. [CrossRef]
31. Ansari, S.; Noori, M.; Pedrood, K.; Mohammadi-Khanaposhtani, M.; Moazzam, A.; Hosseini, S.; Larijani, B.; Adibi, H.; Biglar, M.; Hamedifar, H.; et al. Novel aryl(4-phenylpiperazin-1-yl)methanethione derivatives as new anti-Alzheimer agents: Design, synthesis, in vitro and in silico assays. *J. Mol. Struct.* **2022**, *1262*, 132945. [CrossRef]
32. Kumar, R.R.; Sahu, B.; Pathania, S.; Singh, P.K.; Akhtar, M.J.; Kumar, B. Piperazine, a Key Substructure for Antidepressants: Its Role in Developments and Structure-Activity Relationships. *ChemMedChem* **2021**, *16*, 1878–1901. [CrossRef] [PubMed]
33. Adamczyk-Woźniak, A.; Czerwińska, K.; Madura, I.D.; Matuszewska, A.; Sporzyński, A.; Żubrowska-Zembrzuska, A. Piperazine derivatives of boronic acids—Potential bifunctional biologically active compounds. *New J. Chem.* **2015**, *39*, 4308–4315. [CrossRef]
34. Paneth, A.; Trotsko, N.; Popiolek, Ł.; Grzegorczyk, A.; Krzanowski, T.; Janowska, S.; Malm, A.; Wujec, M. Synthesis and Antibacterial Evaluation of Mannich Bases Derived from 1,2,4-Triazole. *Chem. Biodivers.* **2019**, *16*, e1900377. [CrossRef] [PubMed]
35. Swarnagowri, N.; Santosh, G.L.; Sushruta, S.H.; Swapna, B.; Nitinkumar, S.S. Synthesis, molecular docking and evaluation of library of 3-mercapto-1,2,4-triazole derivatives as antimicrobial agents. *Asian J. Chem.* **2021**, *33*, 3039–3046.