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SYNTHESIS OF 1,2,3-TRIAZOLE CONTAINING DERIVATIVE OF PIPERIDINE

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ABSTRACT
A reductive amination reaction between *N*-Boc -piperidin-4-one and phenoxy-ethylamine was successfully used for the synthesis of (5-Methyl-2-phenyl-2H-[1,2,3] triazol-4ylmethyl)- (2-phenoxy-ethyl)-piperidin-4-yl-amine. The total synthesis of this small molecule is reported for the first time in this study.

KEYWORDS: 1,2,3 triazole**,** Piperidine, Reductive amination.

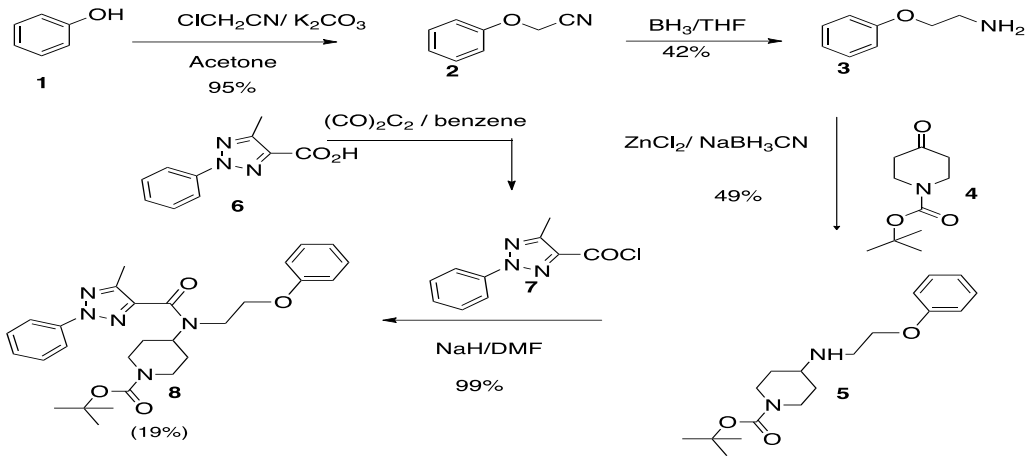
1. INTRODUCTION

Two-thirds of the organic compounds known in the literature are heterocycles.[1] The 1,2,3-triazole nucleus, is one of the most pharmacologically active compounds that exhibits various activities[2] such as, antiviral, anticonvulsant, anti-inflammatory, anticancer, antioxidant, antimicrobial, and antifungal.[3–11] In addition, some 1, 2, 3-triazoles are used in medicinal chemistry and form the basic structure of some drugs available in the market, like tazobactam[12], cefatrizine[13], and carboxyamidotriazole.[12] Moreover, the stability of 1, 2, 3- triazole derivatives in various extreme conditions, acidic and basic media, oxidative and reductive conditions, indicates their aromatic character.[14] Studies have shown that compounds with piperidine rings[15–20] have good selectivity and activity for the P. *falciparum strain*. In the light of the previous information's and in the continuity of our research[21], we report in this paper the synthesis of 1,2,3-triazoles derivative of piperidine. The synthesized triazoles were characterized by spectroscopic techniques, such as ^{1}H NMR, ^{13}C NMR, mass spectra (MS).

2. METERIALS AND METHODS

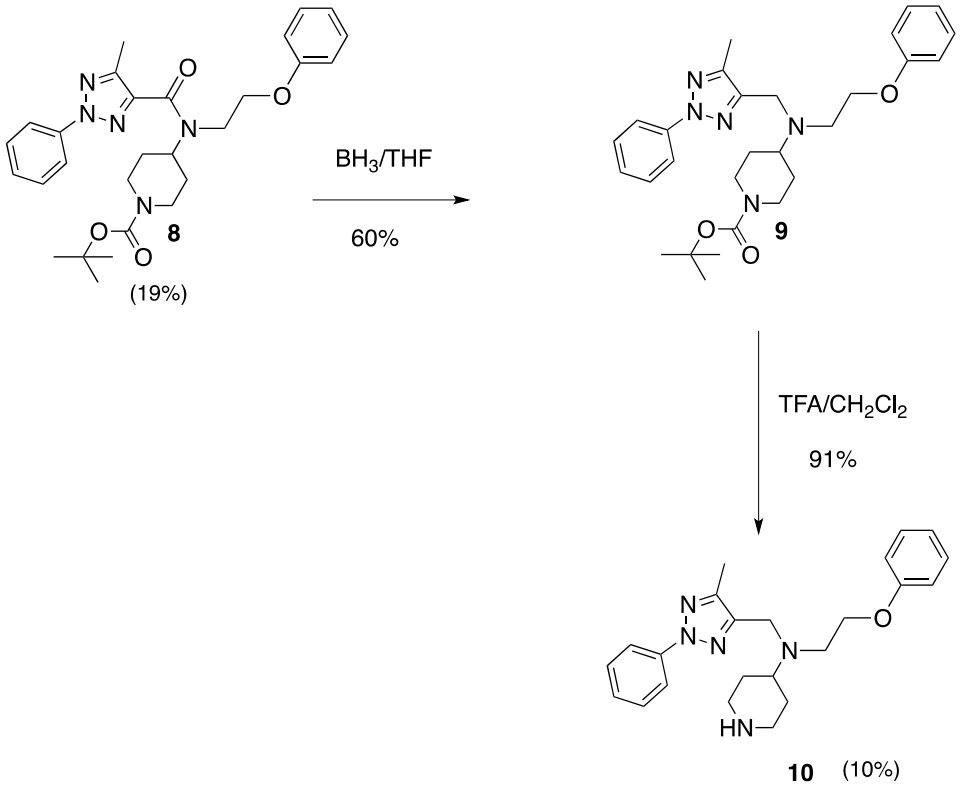
2.1 Method of synthesis of the molecules study

The key compound **10** has been synthesized through a four-step process according to the Scheme 1 and 2. Thus, the condensation of phenol **1** with acetonitrile chloride in acetone at reflux using K_2CO_3, gave compound **2** in 95% yield. Reduction of nitrile **2** using BH_3. THF[22] at 0°C furnished compound **3** (42%). Reductive amination of N-Boc-piperidin-4-one **4** with amine **3** in presence of $NaBH_3CN$[23] gave compound **5** (49%). For the synthesis of compound **8**, we first prepared acyl chloride **7** using $(COCl)_2$.[24] Then the latter without isolated condensed[21] with the compound **5** to give the molecule **8** (99%) (Scheme 1).



Scheme 1: Synthesis of compound 8.

Treatment of the compound **8** with BH_3.THF at 0 ° C gave molecule **9** (60%). To complete the synthesis, compound **9** deprotected[25,26] using trifluoroacetic acid at room temperature provided the triazole **10** (91%) (scheme 2).



Scheme 2: Synthesis of compound 10.

2.2 Experimental Details of the Synthesis of compounds

Experimental section

Commercial reagents were used without purification. Prior to use, CH_3CN, DMSO and Methanol were dried using a pure solvent drying system over aluminum oxide under an argon atmosphere. All anhydrous reactions were carried out under nitrogen atmosphere. Analytical thin layer chromatography was performed on SDS silica gel 60F254 aluminium plates (0.2 mm layer) and was revealed by UV light and/or by phosphomolybdic acid. All flash chromatography separations were performed with SDS silica gel 60. The ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ at ambient temperature on a Bruker AMX 500 spectrometer. Some products secured by DEPT 135, HMQC and HMBC experiments. Chemical shifts are given in δ (ppm) and coupling constants J (Hz) relative to TMS as internal standard; multiplicities were recorded as s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triple), q (quartet) or m (multiplet). Reactions involving anhydrous conditions were conducted in dry glassware under a nitrogen atmosphere. The infrared spectra have been recorded on a spectrometer Perkin- Elmer 842 (reference: polystyrene). GC/MS conditions: Analyses were performed using a 5890-gas chromatogram connected to a G 1019 A mass spectrometer (both from Hewlett Packard) operating in the electro spray ionization mode (ESI).

2-phenoxyacetonitrile (**2**)

A solution of phenol (2g,21.27 mmol) in acetone (15 mL) containing K_2CO_3(3.23g, 23.10 mmol), and acetonitrile chloride (1.6g, 21,27 mmol) was stirred for 12h at reflux. 0.15N NaOH (15 mL) and 15 mL of ethyl acetate were added. The phase separated and the aqueous layer was extacted with ethyle acetate (3x15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate). Yield (2.682, 95%).

Phenoxy-ethylamine (**3**)

A solution of compound **2** (2.642g, 19.86 mmol) in THF (15 mL)) was added BH_3 (1M in THF) (39.72 mL, 39.72 mmol) at 0°C. The reaction mixture was stirred for 2h at room temperature, filtered, and then concentrated in vacuum. The residual is taken in 20 mL of ethyl acetate, washed successively with a saturated solution of NaCl (2x10 mL) and water (2x10 mL). The organic phase was dried over $MgSO_4$ filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane / methanol (90/10) + 5% of triethylamine). Yield: (1.141g, 42 %)

4-*N*-(2-phenoxy-ethyl)-piperidin-1-carboxylic acid ter-butyl ester (**5**)
A solution of compound **3** (1.082g, 7.887 mmol) in methanol (30 mL) containing *t*-butyl-4-oxo-1-piperidine carboxylate (0.786 g, 3.944 mmol), sodium cyanoborohydrure (0.248g, 3.944 mmol), and zinc chlorid (0.268g, 1.972 mmol) was stirred for 48 h at room temperature. 1N NaOH (15 mL) 15 mL of ethyl acetate were added. The phases were separated and the aqueous layer was extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography (ether petroleum / ethyl acetate (8/2)). Yield: (1.076 g, 42%).

4-[(5-Methyl-2-phenyl-2H-[1,2,3,] triazole-4-carbonyl)-(2-phenoxy-ethyl)-amino]piperidine-1-carboxylic acid ter-butyl ester (**8**)
A solution of 4-methyl-2-phenyl-1.2.3-triazole-5-carboxylic acid (0.974g, 4.78 mmol) in benzene 5 mL under argon pressure was added at 0°C (1.208g, 9.56 mmol) of oxalyl chloride to a drop of dimethylformamide. The reaction mixture was stirred for 2h at room temperature and then concentrated in vacuum. In parallel, a solution of compound **5** (0.768g, 2.39 mmol) and sodium hydride (60% in fat, 0.144g, 3.585 mmol) in 5 ml of dimethylformamide is stirred for 45 min at 0 ° C under argon pressure. The acid choride prepared previously is then added to the solution containing compound **5**, the reaction mixture is stirred for 1 hour at 0 ° C. and then the temperature rises to room temperature. After 12 h at room temperature, 10 mL water and 15 mL of ethyl acetate was added. The aqueous layer was extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. The residue was purified by chromatography (ether petroleum / ethyl acetate (8/2 and 6/4)). Yield : (1.208 g, 99%).

4-(4-methyl-2-phenyl-1,2,3-triazole-5-methylene)-N-(2-phenoxy-ethyl)-piperidin-1-carboxylic acid tert-butyl (**9**)
A solution of compound **8** (1.248g, 2.47 mmol) in THF (10 mL)) was added BH_3/THF (1M in THF) (0.53g, 6.17 mmol) at 0°C. The reaction mixture was stirred for 4 h at room temperature, filtered, and then concentrated in vacuum. The residual is taken in 20 mL of ethyl acetate, washed successively with a saturated solution of NaCl (2x10 mL) and water (2x10 mL). The organic phase was dried over $MgSO_4$ filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane / methanol (80/20)). Yield: 0.715g, 60 %)

(5-Methyl-2-phenyl-2H-[1,2,3] triazol-4-ylmethyl)-(2-phenoxy-ethyl)-piperin-4-yl-amine (**10**)
A solution of compound **9** (0.308g 0.626 mmol) in CH_2Cl_2 (2 mL) under argon containing trifluoroacetique acid (1mL 12.85 mmol) was stirred for 12 h at room temperature. After concentration in vacuum, the residual is taken in 5 mL of ethyl acetate then neutralized by $NaHCO_3$ (5%). The aqueous layer was extracted with ethyl acetate (4x5mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated under reduced pressure.

The residue was purified by column chromatography (dichloromethane / methanol (90/10) + 5% of triethylamine). Yield: (0.224g, 91%).

3. RESULTS

3.1 Characteristics of Synthetic Molecules

2-phenoxyacetonitrile **2**
IR (NaCl) cm^{-1}: 2360.65 (CN); MS (ion spray) m/z: 133.0 [M+1]+; RMN ($CDCl_3$, 250 MHz) δ ppm: 4.5 (s, 2 H, CH_2); 6.6-7.3 (m, 5H aromatic); ^{13}C ($CDCl_3$, 62.5 MHz): δ ppm : 53.98 CH_2; 115.45 (2 ×=CH); 123.51 (=CH); 130.44 (2×=CH); 157.04 Cq .

Phenoxy-ethylamine **3**
IR (NaCl) cm^{-1}: 3070.73 (NH_2); MS (ion spray) m/z: 137.0 [M+1]+; RMN ($CDCl_3$, 250 MHz) δ ppm: 1.6 (s large, 2 H, NH_2); 3.1 (t, 2H, J= 6.25 Hz, CH_2), 4.0 (t, 2H, J= 6.25 Hz, CH_2), 6.8-7.4 (m, 5H aromatic); ^{13}C ($CDCl_3$, 62.5 MHz): δ ppm : 41.1 CH_2 ; 70.31 CH_2; 115.45 (2×=CH); 123.51 =CH; 130.44 (2×=CH); 157.04 Cq.

4-*N*-(2-phenoxy-ethyl)-piperidin-1-carboxylic acid ter-butyl *ester* **5**
IR (NaCl) cm^{-1}: 3319.20 (NH); MS (ion spray) m/z: 321.0 $[M+1]^+$; RMN ($CDCl_3$, 250 MHz) δ ppm: 1.1-1.3 (m, 2 H, CH_2); 1.35-1.5 (m, 11H, CH_2, $C(CH_3)_3$) ; 1.7-1.85 (m, 2H, CH_2) ; 2.5-2.8 (m, 3H, CH_2, CH) ; 3.95 (t, 2H, J= 6.37 Hz, CH_2), 3.9-4.1 (m, 3H, CH_2, NH), 6.7-7.3 (m, 5H aromatic); ^{13}C ($CDCl_3$, 62.5 MHz): δ ppm : 28.53 $C(CH_3)_3$; 32.55 (2× CH_2) ; 44.32 (2× CH_2); 45.82 CH_2 ; 54.82 CH ; 67.58 CH_2 ; 79.35 C(CH3)3 ; 115.45 (2×=CH); 123.51 =CH; 130.44 (2×=CH); 157.84 Cq ; 158.80 Cq

4-[(5-Methyl-2-phenyl-2H-[1, 2, 3,] triazole-4-carbonyl)-(2-phenoxy-ethyl)-amino] piperidine-1-carboxylic acid ter-butyl ester **8**
IR (NaCl) cm^{-1}: 1682.37 (amide) ; 1693.36 (ester); MS (ion spray) m/z: 506.0 $[M+1]^+$; RMN ($CDCl_3$, 250 MHz) δ ppm: 1.5 (s, 9 H, $C(CH_3)_3$); 1.7-1.9 (m, 4H, 2× CH_2) ; 2.5 (s, 3H, CH_3) ; 2.6-2.9 (m, 2H, CH_2) ; 3.6-4.1 (m, 2H, CH_2); 4.15-4.4 (m, 2H, 2× CH_2) ; 4.5-4.7 (m, 1H, CH) ; 6.8-8.1 (m, 10H aromatic); ^{13}C ($CDCl_3$, 62.5 MHz): δ ppm : 12.08 and 12.32 CH3 ; 29.11 $C(CH_3)_3$; 30.01 and 31.93 (2× CH_2) ; 42.82 and 45.17 CH_2 ; 44.10 (2× CH_2); 55.45 and 57.19 CH ; 65.95 and 68.35 CH_2 ; 80.35 and 80.47 $C(CH_3)_3$; 114.74 (2×=CH); 118.93 =CH ; 119.04 =CH ; 119.82 =CH ; 121.25 =CH; 121.52 =C ; 128.06 =C ; 129.69 (2×=CH); 139.72 Cq ; 141.49 Cq ; 149.04 and 149.41 Cq ; 155.23 Cq ; 158.92 and 159.19 Cq (amide); 163.57 Cq (ester).

4-(4-methyl-2-phenyl-1,2,3-triazole-5-methylene)-N-(2-phenoxy-ethyl)-piperidin-1-carboxylic acid tert-butyl **9**
IR (NaCl) cm^{-1}: 1724.37 (ester); MS (ion spray) m/z: 492.0 $[M+1]^+$; ^1H RMN ($CDCl_3$, 250 MHz) δ ppm: 1.4 (s, 9 H, $C(CH_3)_3$); 1.6-1.9 (m, 4H, 2× CH_2) ; 2.3 (s, 3H, CH_3) ; 2.5-2.8 (m, 5H, CH, 2×CH_2) ; 3.2- 3.4 (m, 2H, CH_2); 3.7-3.9 (m, 4H, 2× CH_2) ; 6.8-7.9 (m, 10H aromatic); ^{13}C ($CDCl_3$, 62.5 MHz): δ ppm : 18.90 and 19.59 CH_3 ; 25.93 and 26.52 CH_2 ; 36.95 $C(CH_3)_3$; 52.0 (2×CH_2) ; 52.23 and 57.34 CH_2 ; 59.16 and 60.17 CH ; 67.48 and 68.06 CH_2 ; 75.09 and 75.81 CH_2 ; 87.82 and 88.18 $C(CH_3)_3$; 122.87 and 122.87 (3×=CH); 126.59 and 126.69 (2× =CH) ; 129.11 =CH ; 135.08 =CH ; 137.71 and 137.823 (3× =CH); 148.0 and 148.27 Cq ; 153.23 and 154.10 Cq ; 155.75 Cq ; 162.86 and 163.86 Cq ; 166.47 and 167.0 Cq (ester).

(5-Methyl-2-phenyl-2H-[1,2,3] triazol-4-ylmethyl)-(2-phenoxy-ethyl)-piperin-4-yl-amine **10**
IR (NaCl) cm^{-1}: 3443.14 (NH); MS (ion spray) m/z: 392.0 $[M+1]^+$; ^1H RMN ($CDCl_3$, 250 MHz) δ ppm: 1.5-2.0 (m, 4H, 2×CH_2) ; 2.2 (s, 3H, CH_3) ; 2.5-2.9 (m, 5H, CH, 2×CH_2) ; 3.2- 3.4 (m, 2H, CH_2); 3.7-3.9 (m, 4H, 2×CH_2) ; 6.8-8.0 (m, 11H, NH, 10H aromatic); ^{13}C ($CDCl_3$, 62.5 MHz): δ ppm : 10.69 CH_3 ; 30.12 (2×CH_2) ; 45.11 (2×CH2) ; 45.78 CH_2 ; 49.06 CH_2 ; 57.21 CH ; 67.65 CH_2 ; 67.85 CH_2 ; 114.72 (2 ×=CH); 118.62 (2× =CH) ; 121.14 =CH ; 127.13 =CH ; 129.59 (2 × =CH); 129.86 (2 × =CH); 139.97 Cq ; 144.95 Cq ; 145.43 Cq ; 158.80 Cq.

4. CONCLUSION

In this study, we have effectively prepared a new small nitrogen heterocycle with a piperidine and 1,2,3-triazole ring amine scaffolding using flexible chemistry. In six stages, the intermediaries were prepared with good yield. The biological evaluation and the synthesis of its derivatives is currently under investigation in our laboratory and will be described in due course.

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REFERENCES

1. Belen'kii LI, Gramenitskaya VN, Evdokimenkova YBE.The literature of Heterocyclic Chemistry, Part X, 2005-2007. Adv. Heterocycl. Chem., 2011; 102: 1-137.
2. Dheer D, Singh V, Shankar R. Medicinal Attributes of 1,2,3-Triazoles: Current Developments. Bioorg. Chem., 2017; 71: 30-54. DOI: 10.1016/j.bioorg.2017.01.010
3. He YW, Dong CZ, Zhao JY, Ma LL, Li YH, Aisa HA. 1, 2,3-Triazole-containing derivatives of rupestonic acid: Click-chemical synthesis and antiviral activities against influenza viruses. Eur. J. Med. Chem., 2014; 76: 245-255. https://doi.org/10.1016/j.ejmech.2014.02.029
4. Wilhelm EA, Machado NC, Pedroso AB, Goldani BS, Seus N, Moura S, Savegnago L, Jacob RG, Alves D. Organocatalytic synthesis and evaluation of 7-chloroquinoline-1,2,3-triazoyl carboxamides as potential antinociceptive, anti-inflammatory and anticonvulsant agent, *RSC Adv*., 2014; 4: 41437-41445.
5. Lopez-Rojas P, Janecko M, Kubinski K, Amesty A, Maslyk M, Estevez-Braun A, Synthesis and Antimicrobial Activity of 4-Substituted 1,2,3-Triazole-Coumarin Derivatives. Molecules, 2018; 23: 199. https://doi.org:10.3390/molecules23010199.
6. Kurumurthy C, Veeraswamy B, Rao PS, Kumar GS, Rao PS, Reddy VL, Rao JV, Narsaiah B. Synthesis of novel 1,2,3-triazole tagged pyrazolo[3,4-*b*] pyridine derivatives and their cytotoxic activity. Bioorg. Med. Chem. Lett., 2014; 24: 746-749. https://doi.org/10.1016/j.bmcl.2013.12.107
7. Kurumurthy C, Veeraswamy B, Rao PS, Kumar GS, Rao PS, Reddy VL, Rao JV, Narsaiah B. Synthesis of novel 1,2,3-triazole tagged pyrazolo[3,4-*b*] pyridine derivatives and their cytotoxic activity. *Bioorg. Med. Chem. Lett.*, 2014; 24: 746-749. https://doi.org/10.1016/j.bmcl.2013.12.107
8. Zhang HZ, Wei JJ, Kumar KV, Rasheed S, Zhou CH. Synthesis and biological evaluation of novel D-glucose-derived 1,2,3-triazoles as potential antibacterial and antifungal agents. *Med. Chem. Res.*, 2015; 24: 182-196.Su N.-N., Li Y., Yu S.-J., Zhang X., Liu X.-H., Zhao W.-G., Res. Chem. Intermed., 2013; 39: 759-766.
9. Song MX, Deng XQ. Recent developments on triazole nucleus in anticonvulsant compounds: a review. J. Enzym. Inhib. Med. Chem.; 2018; 33: 453-478.
10. Jalal HM. Medicinal and Biological Importance of 1,2,3-Triazoles in Click Chemistry. IJISET, 2015; 2: 901-904.
11. Celik F, Unver Y, Barut B, Ozel A, Sancak K. Synthesis, Characterization and Biological Activities of New Symmetric Bis-1,2,3 Triazoles with Click Chemistry. Med. Chem., 2018; 14: 230-241. doi: 10.2174/1573406413666171120165226.
12. Ramesh S, Ashok D, Goud GL, Reddy VP. Microwave assisted synthesis of novel methylenebis{2-[(1-benzyl/cyclohexyl-1*H*-1,2,3-triazol-4-yl) methoxy] chalcones} and their antibacterial activity. Russ. J. Gen. Chem., 2014; 84: 1608-1614.
13. Ongarora DSB, Strydom N, Wicht K, Njoroge M, Wiesner L, Egan TJ, Wittlin S, Jurva U, Masimirembwa CM, Chibale K. Antimalarial benzoheterocyclic 4-aminoquinolines: Structure-activityrelationship, in vivo evaluation, mechanistic and bioactivation studies. Bioorg. Med. Chem., 2015; 23: 5419-5432.

14. Santos AS, Lukens KA, Coelho L, Noguero F, Wirth DF, Mazitschek R, Moreira R, Paulo A. Exploring the 3-piperidin-4-yl-1H-indole scaold as a novel antimalarial chemotype. Eur. J. Med. Chem., 2015; 102: 320-333.
15. Watson PS, Jiang B, Scott B. A Diastereoselective Synthesis of 2.4-Disubstituted Piperidines: Scaolds for Drug Discovery. Org. Lett., 2000; 2: 3679-3681.
16. Padmanilayam M, Scorneaux B, Dong Y, Chollet J, Matile H, Charman SA, Creek DJ, Charman WN, Tomas ST, Scheurer C. Antimalarial activity of N-alkyl amine, carboxamide, sulfonamide and urea derivatives of a dispiro-1,2,4-trioxolane piperidine. Bioorg. Med. Chem. Lett., 2006; 16: 5542–5545.
17. Meyers MJ, Anderson EJ, McNitt SA, Krenning TM Singh M, Xu J, Zeng W, Qin L, Xu W, Zhao S. Evaluation of spiropip**é**ridine hydantoins as a novel class of antimalarial agent. Bioorg. Med. Chem., 2015; 23: 5144-5150.
18. Misra M, Pandey SK, Pandey VP, Pandey J, Tripathi R, Tripathi RP. Organocatalyzed highly atom economic one pot synthesis of tetrehydropyridines as antimalarials. Bioorg. Med. Chem., 2009; 17: 625-633.
19. Sabbani S, Stocks PA, Ellis GL, Davies J, Hedenstrom E, Ward SA, O'Neill P.M. Piperidine dispiro-1,2,4-trioxane analogues. Bioorg. Med. Chem. Lett., 2008; 18: 5804-5808.
20. Kikuchi H, Tasaka H, Hirai S, Takaya Y, Iwabuchi Y, Ooi H, Hatakeyama S, Kim HS, Wataya Y, Oshima Y. Potent Antimalarial Febrifugine Analogues Against the Plasmodium Malaria Parasite. J. Med. Chem., 2002; 45: 2563-2570.
21. Seck R, Gassama A, Cojean S, Cave C. Synthesis and Antimalarial Activity of 1,4-Disubstituted Piperidine Derivatives. *Molecules*, 2020; 25: 299. doi:10.3390/molecules25020299.
22. Koji F, Shogo Y, Tsutomu M. Reduction of CO_2 to Trimethoxyboroxine with BH_3 in THF. O*rganometallics*, 2014; 33: 6692-6695.
23. Perez-Faginas P, Aranda MT, García-Lopez MT, Infantes L, Fernandez-Carvajal A, Gonzalez-Ros JM, Ferrer-Montiel A, Gonzalez Muniz R. Highly Functionalized 1,2–Diamino Compounds through Reductive Amination of Amino Acid-Derived b–Keto Esters. PLoS ONE, 2013; 8: e53231. doi: 10.1371/journal.pone.0053231.
24. Strazzolini P, Gambi A, Giumanini AG, Vancik H. "The reaction between ethanedioyl (oxalyl) dihalides and $Ag_2C_2O_4$: a route to Staudinger's elusive ethanedioic (oxalic) acid anhydride". J. Chem. Soc., Perkin Transactions 1. 1998; 16: 2553–2558.
25. Hwan LJ. Reduction of a 4-pyrrole phenylacylcontaining peptide with trifluoroacetic acid– triisopropylsilane–phenol–H_2O during solid-phase peptide synthesis and its protein kinase C α inhibitory activity. Bioorg. Med. Chem. Lett., 2005; 15: 2271-2279.
26. Srinivasan N, George AY, Ganesan A. Rapid deprotection of *N*-Boc amines by TFA combined with freebase generation using basic ion-exchange resins. Mol. Divers., 2005; 9: 291-295.