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A Facile Synthesis of Amide Derivatives of [1,2,4]Triazolo[4,3-a]pyridine

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A facile synthesis for preparation of amide derivatives of [1,2,4]triazolo[4,3-a]pyridine can be achieved by the nucleophilic displacement of chloromethyl derivative with methyl amine followed by the reaction with acid analogues in the presence of 1-[*bis*(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU). Reaction of 2-chloropyridine with hydrazine hydrate (99 %) gave 2-hydrazinopyridine (**2**). Compound **3** was obtained in good yields by treating 2-hydrazinopyridine with chloroacetyl chloride. Further 3-chloromethyl-[1,2,4]triazolo[4,3-a]pyridine (**4**) is obtained by treatment of compound **3** with $POCl_3$. Nucleophilic displacement of compound **4** with methyl amine gave methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine (**5**). Finally protecting and deprotecting of compound **5** with Boc anhydride and HCl in dioxane gives hydrochloride salt of compound **5** *i.e.* (**6**) The reaction of hydrochloride salt of methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine with 10 different acids yields amide analogues.

Keywords: *s*-Triazolo pyridines, Pyridine derivatives, 1,2,4-Triazolo[4,3-a]pyridine, Triazolo derivatives.

INTRODUCTION

Pyrolo, imidazo- and triazolo pyridines belonging to class of N-bridge head 5,6-bicyclic heterocycles are important motifs in bio-medicinal chemistry due to their good SAR (structure-activity relationship). Among them *s*-triazolo(4,3-a)pyridine ring system (**I**) that has been known since several years but to which meager attention has been paid. An effort was initiated to develop the synthesis amido aminomethyl fused triazoles (**II**) that would be compatible with amino acid substrates and polar functional groups.

A wide range of research was going on these derivatives because of their interesting biological activities like anti-microbial [1], antiviral [1], anticonvulsant [1], antifungal [1], anticancer [1], antiallergic [2], herbicide activity [3], anti-oxidants [1]. These fused triazoles with general formula **I** are specially shows gastrointestinal [4] and chemotherapeutic activity [4-6] due to their outstanding effectiveness against a wide range of micro-organisms, such as, *Staphylococcus aureus*, *Escherichia coil*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*. These derivatives are used in the treatment of schistosomiasis [7] a typical disease found in Egypt. These 1,2,4-triazolo[4,3-a]pyridine derivatives have a considerable effect on glutamate [8,9]. This helps us to cure neurological and psychiatric disorders, which are associated with glutamate dysfunction. Triazolopyridines are found in MAP kinase inhibitors [10-12] and secretagogues, which is a growth hormone. There are reports on some classes of 1,2,4-triazolo[4,3-a]pyridine derivatives can be used as p38α inhibitors [10-13]. They are useful in the treatment of inflammation, osteo-arthritis, rheumatoid arthritis, cancer, reperfusion or ischemia in stroke or heart attack, autoimmune diseases and other disorders. Some biologically active molecules containing [1,2,4]triazolo-[4,3-a]pyridine as a core moiety are represented in Fig. 1.

There are several methods for the preparation of amino methyl derivatives. Decarboxylation of α-heteroaryl glycines, reduction of methyl azides, nitriles and aldoximes are some of them. To the best of our knowledge there are few reports available for the synthesis of amino methyl substituted 1,2,4-triazolo[4,3-a]pyridine, especially on our target molecule methyl[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine (**V**).

Several synthetic approaches were known for the synthesis of 3-chloromethyl-[1,2,4]triazolo[4,3-a]pyridine (**III**) [4] and [1,2,4]triazolo[4,3-a]pyridin-3-yl-ethylamine (**IV**) [14] and fewer number of synthetic approaches are known for methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine (**V**) and ours is a novel approach. But amide derivatives of **V** were not reported yet. Intermediate 5 may be prepared by Mitsunobu reaction [15]. This reaction can be carried out in the presence of triphenyl phospine, diethyl azodicarboxylate (DEAD) and TMS cyanide as an additive. But this procedure is complicated and involves hazardous regent TMS cyanide. We synthesized

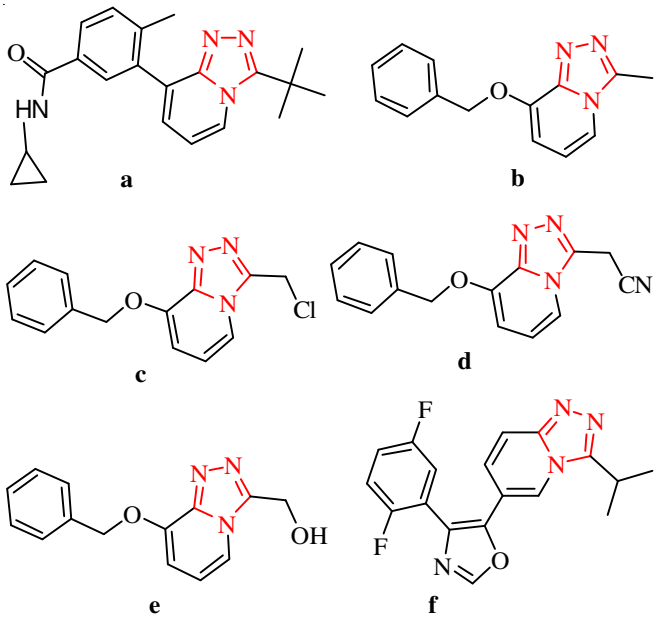


Fig. 1. Biologically active molecules containing [1,2,4]triazolo[4,3-a]pyridine as a core moiety

methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine (**V**) in a economical way by using 2 M methyl amine/THF. After preparing compound **7** we planned a methodology, which involves acid amine coupling. In this methodology we will get compounds with chemical formula **II**.

Bearing these results in mind, we have designed and synthesized a new variety of amide derivatives of [1,2,4]triazolo[4,3-a]pyridine.

Due to their high structure activity relationship values N-(heteroarylmethyl)aromatic amides were falls under important class of bioactive compounds [16] *i.e*. amino methyl derivatives containing pyridine, thiophene, pyrazene and other heterocyclic systems possess high potency of biological activity.

EXPERIMENTAL

Fig. 2 depicts the synthetic route for the preparation hydrochloride salt of methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine (**7**). 2-Chloro pyridine was treated with hydrazine hydrate (99 %) at 100 °C for 48 h to yield hydrazine derivative of pyridine (**2**) [2,5,7,9,17,18]. Compound **2** was selectively mono acylated with chloroacetyl chloride to afford amide derivative (**3**) of compound **2** [2,9,17,18]. Further, compound **3** was cyclized with $POCl_3$ with the elimination of water molecule to afford 3-chloromethyl-[1,2,4]triazolo[4,3-a]-pyridine (**4**) [4,17]. Further, compound **4** is converted to methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine (**5**) by treating with 2 M methyl-amine in methanol. As compound **5** was unable to purify at that stage hence it was protected with $(Boc)_2O$ to give methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-carbamic acid *tert*-butyl ester (**6**). Finally, compound **6** was deprotected with HCl/dioxane to afford hydrochloride salt of methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine (**7**).

Fig. 3 illustrates the synthesis of amide derivative of methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine (**7**). In this reaction we used 1-[*bis*(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) as a peptide coupling reagent and N,N-diisopropylethylamine (DIPEA) as a base in DMF solvent. A series of amide derivatives were prepared by using above condition with good yields and purity.

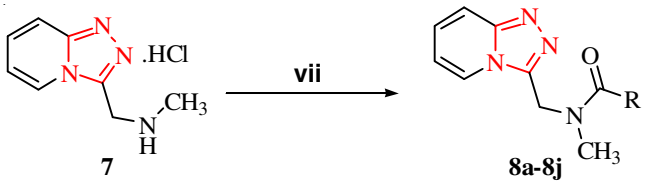


Fig. 3. Synthesis of N-(heteroarylmethyl)aromatic amide

All reagents were purchased from commercial sources and were used as received. ^{1}H NMR spectra were obtained on a AGILENT 300 spectrometer at 300 MHz or AGILENT 400 spectrometer at 400 MHz with tetramethylsilane used as an internal reference. Thin-layer chromatography (TLC) was performed using Whatman No. 4500-101 (Diamond No. MK6F silica-gel 60 Å) plates. Visualization of TLC plates was performed using UV light (254 nm). LCMS was obtained on the Column: X Bridge C18 (100 mm × 4.6 mm) 3.5 µm.

Synthesis of pyridin-2-yl-hydrazine (2): To a stirred solution of **1** (20 g, 0.176 mol, 1 equiv) in hydrazine hydrate (200 mL, 10 vol) was stirred at 100 °C for 48 h. When TLC (8:2 EtOAc and methanol) showed complete consumption of the starting material, the reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (5 × 500 mL), dried over Na_2SO_4 evaporated to dryness under reduced pressure to afford **2** (15.0 g, 78 %) as a red oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (1H, d, J = 3 Hz, Ar-H), 7.51-7.45 (1H, m, Ar-H), 6.71-6.66 (2H, m, Ar-H), 5.78 (1H, brs, -NH), 3.81 (2H, brs, $-NH_2$); LCMS calculated for $C_5H_7N_3$: 109.13; Found 110.1, $[M+H]^+$

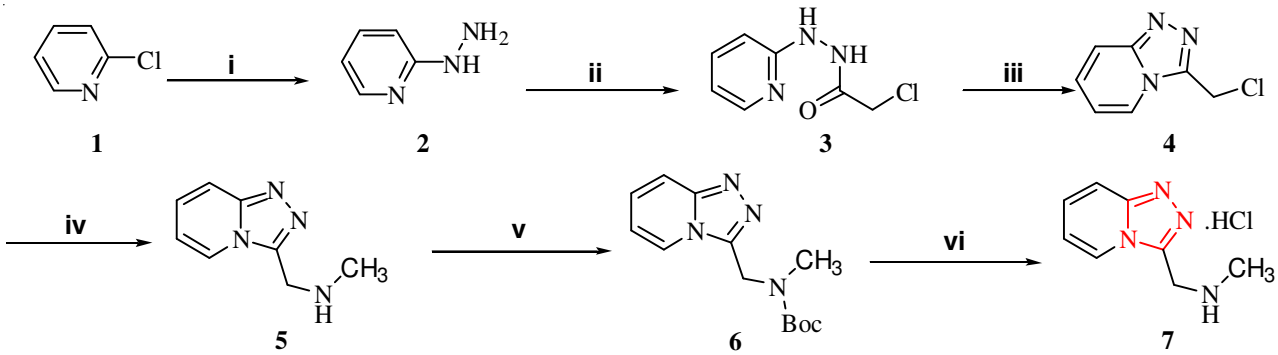


Fig. 2. Synthesis of hydrochloride salt of methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine

Synthesis of chloro-acetic acid N'-pyridin-2-yl-hydrazide (3): To a stirred solution of compound **2** (5 g, 1 equiv) in dichloromethane (100 mL) was added chloroacetyl chloride (4.19 mL, 1.1 equiv) drop wise at 0 °C with vigorous stirring. After completion of addition formation of white precipitate was observed, this was stirred at ambient temperature for 12 h. When TLC (9:1 EtOAc and methanol) showed complete consumption of the starting material, the reaction mixture was filtered and the obtained solids were washed with dichloromethane (30 mL), solids were dissolved in water (50 mL) and basified (pH 8.0) with sat. $NaHCO_3$ and extracted with dichloromethane (3 × 100 mL), dried over Na_2SO_4, evaporated under reduced pressure to afford compound **3** (5.00 g, 58 %) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.87 (1H, brs, -NH), 10.59 (1H, brs, -NH), 8.07-8.00 (2H, m, Ar-H), 7.13-7.03 (2H, m, Ar-H), 4.3 (2H, s, -CH_2Cl); LCMS calculated for $C_7H_8N_3OCl$: 185.61; Found 186 $[M+H]^+$.

Synthesis of 3-chloromethyl-[1,2,4]triazolo[4,3-a]-pyridine (4): Under inert atmosphere $POCl_3$ (25 mL, 5 vol) was slowly added to compound **3** (5 g, 0.027 mol) at ambient temperature, the resulting reaction mixture was stirred at 120 °C for 12 h. Reaction was monitored by TLC (9:1 EtOAc/methanol), which showed complete consumption of the starting material, $POCl_3$ was evaporated completely, the crude was basified with sat. $NaHCO_3$. The aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, evaporated under reduced pressure to afford crude product. The crude was triturated with ether to afford compound **4** (2.5 g, 55.55 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (1H, d, *J* = 8 Hz, Ar-H), 7.84 (1H, d, *J* = 8 Hz, Ar-H), 7.39-7.34 (1H, m, Ar-H), 7.00-6.97 (1H, m, Ar-H), 5.18 (2H, s, -CH_2Cl). LCMS calculated for $C_7H_6N_3Cl$: 167.60; Found 168.08, 170.08, [M], $[M+2]^+$.

Synthesis of methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine (5): To a stirred solution of compound **4** (2.50 g, 1.0 equiv) in MeOH (20 mL), was added 2 M solution of methyl amine in methanol (3 mL) at ambient temperature. The reaction mixture was stirred at the same temperature for 12 h. Reaction was monitored by TLC (9:1 EtOAc and methanol) which showed complete consumption of the starting material, the reaction mixture was evaporated under reduced pressure, dried completely to give crude compound **5** (2.3 g) as a red liquid.

Synthesis of methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-carbamic acid *tert*-butyl ester (6): To a stirred solution of compound **5** (2.30 g, 1.0 equiv) in THF (20 mL) was added Boc anhydride (3.85 mL, 1.1 equiv) at ambient temperature. The reaction mixture was stirred at the same temperature for 12 h. Reaction was monitored by TLC (8:2 EtOAc and methanol) which showed complete consumption of the starting material, the reaction mixture was evaporated, obtained crude was dissolved in water (20 mL). The aqueous layer was initially extracted with pet. Ether (2 × 20 mL) to remove excess Boc anhydride. Further the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, evaporated under reduced pressure to afford crude product. The crude was triturated with ether to afford **6** (2.0 g, 54.0 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (1H, brs, -NH-Boc), 7.77 (1H, d, *J* = 12 Hz, Ar-H), 7.29 (1H, d, *J* = 8 Hz, Ar-H), 6.86 (1H, t, *J* = 6 Hz, Ar-H), 5.02 (2H, s, -NCH_2), 2.65 (3H, -s, -NCH_3), 1.49 (9H, s, *t*-Bu) MS, LCMS calculated for $C_{13}H_{18}N_4O_2$: 262.31; Found 263.19 $[M + H]^+$.

Synthesis of hydrochloride salt of methyl-[1,2,4]triazolo-[4,3-a]pyridin-3-ylmethylamine (7): To a stirred solution of compound **6** (2 g, 1 equiv) in dioxane (10 mL) was added 2 M HCl in dioxne (10 mL) at ambient temperature. The reaction mixture was stirred at the same temperature for 12 h. Reaction was monitored by TLC (8:2 EtOAc and methanol) which showed complete consumption of the starting material, the reaction mixture was evaporated under reduced pressure to dryness and the obtained crude was triturated with ether to afford compound **7** (1.3 g, 86 %) as brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.61 (2H, brs, -NHHCl), 8.80 (1H, d, *J* = 6.4, Ar-H), 7.89 (1H, d, *J* = 9.2, Ar-H), 7.56-7.53 (1H, t, *J* = 6.8, Ar-H), 7.18-7.15 (1H, t, *J* = 6.4, Ar-H), 4.79 (2H, s, -NCH_2), 2.70 (3H, s, -NCH_3); LCMS calculated for $C_8H_{11}N_4Cl$: 162.14; Found 163.21 $[M + H]^+$.

General synthetic procedure for synthesis of amide derivatives of methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethylamine (8a-8k): To a stirred solution of compound **7** (100 mg, 1.0 equiv) in DMF (3 mL) was added 4-bromo-2-methyl-benzoic acid (241.32 mg, 1.1 equiv). To this mixture DIPEA (0.526 mL, 3.0 equiv) followed by HATU (387.84 mg, 1.0 equiv) were added at ambient temperature. The reaction mixture was stirred at the same temperature for 2 h. Reaction was monitored by TLC (8:2 EtOAc and methanol), which showed complete consumption of the starting material. The reaction mixture was basified with sat. $NaHCO_3$. The aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford crude product. The crude was purified by silica-gel (100-200) column chromatography using 5 % methanol/ethylacetate as an elluent to afford 4-bromo-2,N-dimethyl-N-[1,2,4]triazolo[4,3-a]-pyridin-3-ylmethyl benzamide (**8a**) (30 mg, 70 %) as a off-white solid. Same procedure was adopted for the synthesis of remaining compounds **8b-8k**.

Spectral data

4-Bromo-N-dimethyl-N-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-benzamide (8a): Yield 38 %, Off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.74 (1H, d, *J* = 8 Hz, Ar-H), 7.82 (1H, d, *J* = 6 Hz, Ar-H), 7.39-7.36 (3H, m, Ar-H), 7.19 (1H, d, *J* = 6 Hz, Ar-H), 6.94 (1H, t, *J* = 8 Hz, Ar-H), 5.31 (2H, s, N-CH_2), 2.88 (3H, s, N-CH_3), 2.13 (3H, s, Ar-CH_3); LCMS calculated for $C_{16}H_{15}N_4OBr$: 359.22; Found 361.08 $[M + 2]^+$.

4-Methoxy-N-methyl-N-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-benzamide (8b): Yield 33 %, Off-brown solid. ^{1}H NMR ((300 MHz, $CDCl_3$, ppm): δ8.76 (1H, d, *J* = 6 Hz, Ar-H), 7.79 (1H, d, *J* = 9 Hz, Ar-H), 7.29-7.25 (3H, m, Ar-H), 693-6.91 (3H, m, Ar-H), 5.30 (2H, s, N-CH_2), 3.82 (3H, s, O-CH_3), 3.05 (3H, s, N-CH_3); LCMS calculated for $C_{16}H_{16}N_4O_2$: 296.32; Found 297.21 $[M + 1]^+$.

4-N-Dimethyl-N-[1,2,4]triazolo[4,3-a]pyridin-3-yl-methyl-benzamide (8c): Yield 34 %, red gummy solid. ^{1}H

NMR ((300 MHz, $CDCl_3$, ppm): δ8.76 (1H, d, *J* = 6, Ar-H), 7.79 (1H, d, *J* = 9.3, Ar-H), 7.33-7.31 (3H, m, Ar-H), 7.21-7.18 (2H, m, Ar-H), 6.91-6.87 (1H, t, *J* = 6.6, Ar-H), 5.30 (2H, s, N-CH_2), 3.05 (3H, s, N-CH_3), 2.37 (3H, s, Ar-CH_3); LCMS calculated for $C_{16}H_{16}N_4O$: 280.32; Found 281.18 $[M + 1]^+$.

3-Mercapto-N-methyl-N-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl benzamide (8d): Yield 30 %, brown gummy liquid. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ8.51 (1H, s, Ar-H), 7.92 (1H, d, *J* = 12 Hz, Ar-H), 7.56-7.35 (6H, m, Ar-H), 7.04 (1H, s, Ar-H), 5.17 (2H, s, N-CH_2), 2.84 (4H, s, N-CH_3, SH); LCMS calculated for $C_{15}H_{14}N_4OS$: 298.09; Found 298.22 $[M]^+$.

4-Bromo-2-fluoro-N-methyl-N-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl benzamide (8e): Yield 22 %, white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (1H, d, *J* = 6 Hz, Ar-H), 7.80 (1H, d, *J* = 9 Hz, Ar-H), 7.39-7.29 (3H, m, Ar-H), 7.28-7.21 (1H, m, Ar-H), 6.09 (1H, t, *J* = 9, Ar-H), 5.32 (2H, s, N-CH_2), 2.95 (3H, s, N-CH_3); LCMS calculated for $C_{15}H_{12}N_4OBrF$: 363.18; Found 363.22, 365.20, [M], $[M + 2]^+$.

2,N-Dimethyl-N-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl isonicotinamide (8f): Yield 28 %, Off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (1H, d, *J* = 6 Hz, Ar-H), 8.58 (1H, d, *J* = 6 Hz, Ar-H) 7.81 (1H, d, *J* = 9 Hz, Ar-H), 7.36-7.30 (1H, m, Ar-H), 7.12 (1H, s, Ar-H), 7.06 (1H, d, *J* = 4.2 Hz, Ar-H), 6.95-6.91 (1H, t, *J* = 6 Hz, Ar-H), 5.29 (2H, s, N-CH_2), 3.03 (3H, s, N-CH_3), 2.58 (3H, s, Ar-CH_3); LCMS calculated for $C_{15}H_{15}N_5O$: 281.31; Found 282.20 $[M + H]^+$.

4-Formyl-3-hydroxy-N-methyl-N-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl benzamide (8g): Yield 38 %, Brown solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 10.87 (1H, s, -CHO), 10.29 (1H, s, -OH), 8.55 (1H, d, *J* = 4 Hz, Ar-H), 7.81-7.70 (2H, dd, J 1 = 8 Hz, *J* 2 = 8 Hz, Ar-H), 7.42 (1H, d, *J* = 8 Hz, Ar-H), 7.08-6.95 (3H, m, Ar-H), 5.21 (2H, s, -N-CH_2), 2.92 (3H, s, -NCH_3); LCMS calculated for $C_{16}H_{14}N_4O_3$: 310.31; Found 311.15 $[M + H]^+$.

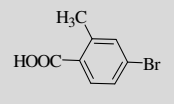
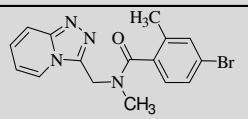
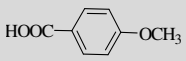
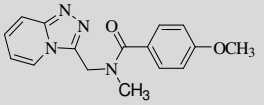
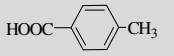
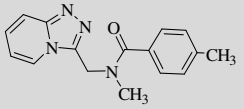
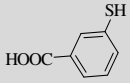
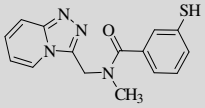
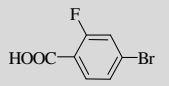
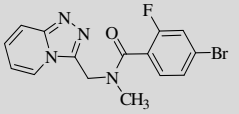
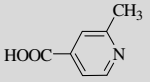
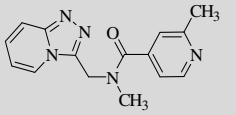
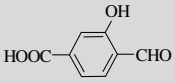
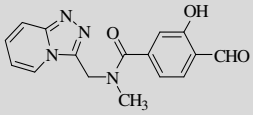
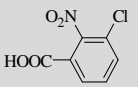
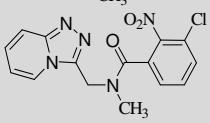
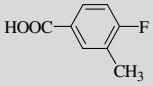
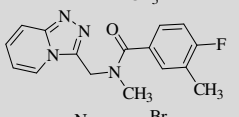
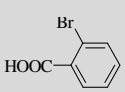
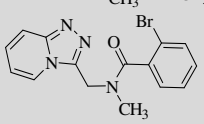
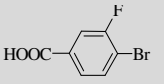
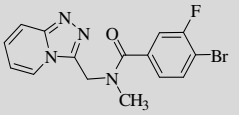
3-Chloro-N-methyl-2-nitro-N-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl benzamide (8h): Yield 40 %, White solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ8.63 (1H, d, *J* = 7.2 Hz, Ar-H), 8.17 (1H, d, *J* = 8.8 Hz, Ar-H), 7.80 (1H, d, *J* = 9.2 Hz, Ar-H), 7.57-7.54 (1H, dd, *J1* = 4 Hz, *J2* = 8 Hz, Ar-H), 7.40 (1H, d, *J* = 4 Hz, Ar-H), 7.36-7.34 (1H, m, Ar-H), 6.94-6.91 (1H, t, *J* = 4 Hz, Ar-H), 5.39 (2H, s, -NCH_2), 2.82 (3H, s, -NCH_3).

4-Fluoro-3,N-dimethyl-N-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl benzamide (8i): Yield 53 %, Off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ8.76 (1H, d, *J* = 6.4 Hz, Ar-H), 7.79 (1H, d, *J* = 8.0 Hz, Ar-H), 7.36-7.33 (3H, m, Ar-H) 7.02 (1H, d, *J* = 9 Hz, Ar-H), 6.95 (1H, d, *J* = 7.2 Hz, Ar-H), 5.30 (2H, s, -NCH_2), 3.05 (3H, s, -NCH_3), 2.25 (3H, s, Ar-CH_3), LCMS calculated for $C_{16}H_{15}N_4OF$: 298.31; Found 299.24 $[M + H]^+$.

2-Bromo-N-methyl-N-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl benzamide (8j): Yield 40 %, Off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ8.74 (1H, d, *J* = 9 Hz, Ar-H), 7.79 (1H, d, *J* = 9 Hz, Ar-H), 7.56-7.53 (1H, dd, *J1* = 1.2 Hz, *J2* = 6 Hz, Ar-H), 7.40-7.24 (4H, m, Ar-H), 6.58 (1H, brs, -NCH), 5.10 (1H, brs, -NCH), 2.79 (3H, s, -NCH_3); ^{13}C NMR (400 MHz, DMSO-d_6, ppm): δ168.54 (-NC=O), 149.68 (Ar-C), 142.87 (Ar-C), 137.44 (Ar-C), 132.53 (Ar-C), 130.85 (Ar-C), 127.95 (Ar-C), 124.48 (Ar-C), 117.96 (Ar-C), 115.21, Ar-C), 113.56 (Ar-C), 40.12 (-NCH_2), 35.45 (-NCH_3); LCMS calculated for $C_{15}H_{13}N_4OBr$: 345.19; Found 344.99,346.88, [M], $[M + 2]^+$.

4-Bromo-3-fluoro-N-methyl-N-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl benzamide (8k): Yield 43 %, Off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ8.69 (d, 1H, *J* = 6 Hz, Ar-H), 7.80 (d, 1H, *J* = 9 Hz, Ar-H), 7.63-7.58 (m, 1H, Ar-H), 7.35-7.29 (1H, m, Ar-H), 7.20 (1H, d, *J* = 9 Hz, Ar-H), 7.09 (1H, d, *J* = 8.1 Hz, Ar-H), 6.93-6.89 (1H, m, Ar-H), 5.27 (2H, s, -NCH_2), 3.08 (3H, s, -NCH_3); ^{13}C NMR (400 MHz, DMSO-d_6, ppm): δ169.49 (-NC=O), 159.11 (Ar-C), 156.66 (Ar-C), 149.51 (Ar-C), 142.96 (Ar-C), 133.76 (Ar-C), 128.02 (Ar-C), 124.73 (Ar-C), 115.69 (Ar-C), 113.76 (Ar-C), 109.77 (Ar-C), 40.10

TABLE-1
PHYSICAL DATA OF COMPOUNDS **8a-8k**

Compd.	Acid	Product	Time (h)
8a			2
8b			2
8c			2
8d			2
8e			2
8f			2
8g			2
8h			2
8i			2
8j			2
8k			2

(-NCH_2), 36.90 (-NCH_3); LCMS calculated for $C_{15}H_{12}N_4OBrF$: 363.18 Found 363.22,365.20, [M], $[M + 2]^+$.

RESULTS AND DISCUSSION

The key step in present research is the replacement of chloro with methyl amine. It was assumed to be nucleophilic substitution of order 2.The methyl amine replaces the chloro in a concerted mechanism *i.e.* while the methyl amine attacks the electron deficient carbon, at the same time chloro leaves the carbon. Because of the high polarity and solubility issues obtained amine was protected with Boc anhydride to purify, later de protected to get hydrochloride salt of that amine.

Hydrochloride salt of methyl-[1,2,4]triazolo[4,3-a]pyridin-3-ylmethyl-amine (**7**) was treated with various acid derivatives in the presence of DIPEA and HATU in DMF at ambient temperature to afford the amide derivatives **8a-8k**. This method has the advantages of easier work-up, mild reaction conditions.

The amidic products were confirmed by NMR, mass and ^{13}C NMR spectral techniques. In the 300 MHz ^1H NMR spectra of derivatives **8j**, **8k** (in $CDCl_3$), the following signals were detected. Peaks at δ 8.74-6.89 for aromatic protons, singlet's at δ 6.58-5.24 corresponds to -NCH_2 protons and a singlet at δ 2.78-3.08 represent -NCH_3 protons. In ^{13}C NMR (400 MHz, DMSO-d_6, ppm), the following signals were detected. A peak at δ 168.54-168.49 corresponds to C=O of amide and a peak at δ 36.90-35.45 corresponds to -NCH_3 carbon. A peak at δ 40 corresponds to -NCH_2 carbon. A series of peaks from δ 159.11-109.56 represents aromatic carbons. Besides NMR studies, mass spectra displayed the exact molecular ion peaks in positive mode. The yields and physical data of the final compounds are given in Table-1.

Conclusion

The present study involves the synthesis of the novel series of [1,2,4]triazolo[4,3-a]pyridine derivatives by adopting a simple and versatile synthetic methodology. From the previous results, we are expecting our newly designed molecules may be biologically active. Thus, this novel class of amide derivatives of [1,2,4]triazolo[4,3-a]pyridine core represents the worthy hit compounds, which can be a basis for further investigations and development of novel potent agents.

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