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Research Article

Synthesis and characterization of new iminopyridazine butyronitrile hydrobromides

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ABSTRACT

In this study, general methods were applied for the preparation of new iminopyridazinebutyronitriles. A series of six new 4-(3-aryl-1,6-dihydro-6-iminopyridazin-1-yl)butyronitrilehydrobromides **(2a-2f) (Scheme 1)** have been prepared starting from commercially available 3-amino-6-chloropyridazine in two steps with good yields. The synthesized compound's were characterized by IR, ^{1}H NMR and high-resolution structures mass structures spectral (HRMS) data.

Introduction

Heterocyclic compounds having pyridazine moiety have been reported as important biologically active substances in the pharmaceutical and agrochemical areas due to their wide applications as safe and effective drugs (Zou et al., 2002; Kandile et al., 2009; Mantu et al., 2010; Flefel et al., 2017). These valuable biological activities depend upon the variation of substitutional groups in pyridazinering system. γ-Aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the brain responsible for normal brain function (Sivilotti and Nistri, 1991; Oslen and Sieghart, 2009). The ionotropic GABA receptor, which mediates the fast synaptic inhibition, belongs to the Cys-loop receptor family (Sine and Engel, 2006) (Fig. 1).

The pyridazine backbone is a part of the structures of GABA receptor antagonists such as Minaprine, SR 95103 (Wermuth et al., 1987), Gabazine (Chambon et al., 1985; Ueno et al., 1997), SR 95813 (Yamamoto et al. 2012), etc. (Fig. 2). The aryl pyridazine scaffold in the iminopyridazine GABA analogs plays a vital role in acting as a GABA receptor antagonist. Several amino pyridazine analogs act as GABA receptor competitive antagonists in mammals and parasites (Wermuth et al., 1987; Duittoz and Martin, 1991; Martin et al., 1995).

Gabazine-based iminopyridazines reported functioning as competitive antagonists in mammalian and insect GABA receptors (Iqbal et al., 2011; Rahman et al., 2012; Rahman et al., 2014).

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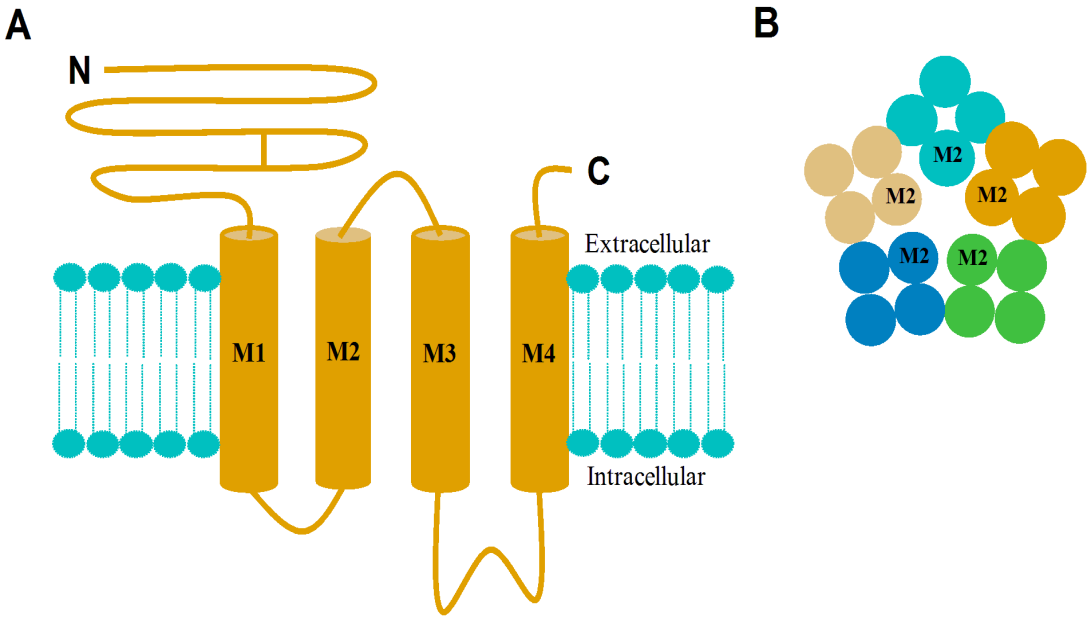


Fig. 1. Schematic representation of a Cys-loop receptor. (A) Side view. (B) Top view. Transmembrane segments are labeled as M1, M2, M3, and M4. An extended intracellular loop is shown between M3 and M4.

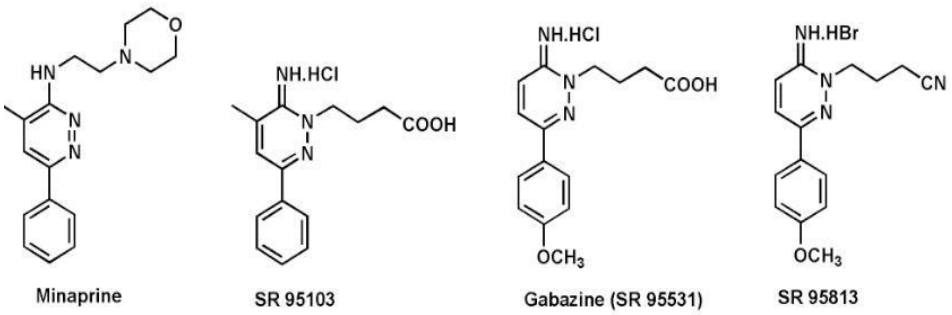


Fig. 2. Structures of Minaprine, SR 95103, Gabazine (SR 95531) and SR 95813, examples of GABA receptor antagonists based on pyridazine backbone.

A bioisosterism is an approach to designing of new drugs by the particular modification of lead compounds (Lima and Barreiro, 2005). The bioisosteric replacement of the carboxyl group of gabazine (SR 95531) by nitrile group (SR 95813) increased the antagonistic activity in ρ1 receptor (Yamamoto et al., 2012). This particular information prompted us to synthesize some new iminopyridazine butyronitrile derivatives taking gabazine

(Fig. 2) as a lead compound, in which the 3-position of pyridazine ring was replaced by various aromatic substituents and the carboxylic group of GABA part was exchanged by nitrile group (**Scheme 1**). The synthesized compound's structures were characterized using different spectroscopic methods (IR, ^{1}H NMR and HRMS data).

Materials and Methods

Experimental

An SMP10 apparatus was used to determine the melting points of the synthesized compounds and are uncorrected. Infrared spectra were recorded on the SHIMADZU IR Tracer-100 infrared spectrometer within the range of 4000-400 cm^{-1} and were recorded as KBr pellets. A BRUKER 400 MHz NMR spectrometer was used to record ^{1}H NMR spectra in $CDCl_3$ and DMSO-d_6. Chemical shifts (δ values) are given in ppm and tetramethylsilane (TMS) was used as an internal standard. The *J* values are given in Hertz. Spin multiplicities are expressed as follows: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), and m (multiplet). The high-resolution mass spectra (HRMS) were measured at the analytical center of Kumamoto University, Kumamoto, Japan. Reagents were purchased from TCI Chemical Industries, Ltd (India) and are used without further purification.

General procedure for the synthesis of 3-amino-6-arylpyridazines (1a-1f)

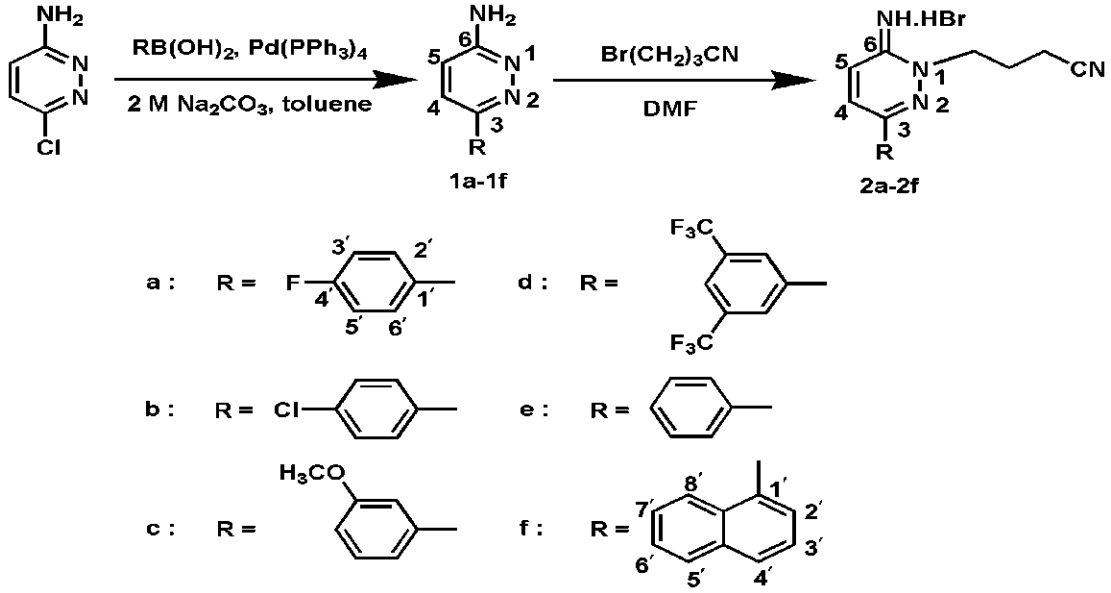
A mixture of 3-amino-6-chloropyridazine (259 mg, 2.0 mmole), an arylboronic acid (2.2 mmole), tetrakis(triphenylphosphine)palladium (0) (70 mg), 2 M aq. Na_2CO_3 solution (2.2 mL) and toluene (20 mL) were placed in a reaction vessel and stirred in a nitrogen atmosphere for 30 min at room temperature. The reaction mixture was then refluxed with stirring until the completion of the reaction (checked by TLC) in an inert condition. After completing the reaction, the mixture was allowed to cool and evaporated using a rotary vacuum evaporator. 60 mL EtOAc was added to the residue and it was placed in an ultrasonic bath for 5 min. The mixture was filtered and washed thoroughly with EtOAc (150 mL). The filtrate was evaporated to dryness using a rotary vacuum evaporator. The residue was purified by silica gel column chromatography to obtain 3-amino-6-arylpyridazines **1a-1f**.

3-Amino-6-(4-flurophenyl)pyridazine (1a). Yield (185.2 mg, 49%); R_f = 0.61 (EtOAc); mp 117-119 °C; IR (KBr): ν cm^{-1} 3400 (N-H stretch), 3120 (N-H stretch), 1620 (N-H bend); ^{1}H NMR (DMSO-d_6): δ ppm 7.99 (2H, d, *J* = 8.8 Hz, H-3′, H-5′), 7.86 (1H, d, *J* = 9.6 Hz, H-4), 7.29 (2H, d, *J* = 8.8 Hz, H-2′, H-6′), 6.84 (1H, d, *J* = 9.2 Hz, H-5), 6.49 (2H, s, NH_2). FAB HRMS (acetone/NBA) calcd. for $C_{10}H_9N_3F$ 190.0781 $[M+H]^+$. Found 190.0781.

3-Amino-6-(4-chlorophenyl)pyridazine (1b). Yield (119.2 mg, 29%); R_f = 0.74 (EtOAc); mp 168-170 °C; IR (KBr): ν cm^{-1} 3400 (N-H stretch), 3180 (N-H stretch), 1660 (N-H bend); ^{1}H NMR (DMSO-d_6): δ ppm 7.98 (2H, d, *J* = 8.0 Hz, H-3′, H-5′), 7.81 (1H, d, *J* = 9.2 Hz, H-4), 7.51 (2H, d, *J* = 8.4 Hz, H-2′, H-6′), 6.84 (1H, d, *J* = 9.1 Hz, H-5), 6.53 (2H, s, NH_2). FAB HRMS (acetone/NBA) calcd. for $C_{10}H_9N_3Cl$ 206.0485 $[M+H]^+$. Found 206.0474.

3-Amino-6-(3-methoxyphenyl)pyridazine (1c). Yield (92.5 mg, 23%), R_f = 0.70 (EtOAc); mp 125-127 °C; IR (KBr): ν cm^{-1} 3400 (N-H stretch), 3200 (N-H stretch), 1650 (N-H bend); ^{1}H NMR (DMSO-d_6): δ ppm 7.80 (1H, d, *J* = 9.2 Hz, H-4), 7.50-7.62 (2H, m, H-2′, H-4′), 7.34-7.38 (1H, m, H-5′), 6.95 (1H, d, *J* = 6.8 Hz, H-6′), 6.83 (1H, d, *J* = 9.6 Hz, H-5), 6.48 (2H, s, NH_2), 3.81 (3H, s, OCH_3). FAB HRMS (acetone/NBA) calcd. for $C_{11}H_{12}N_3O$ 202.0980 $[M+H]^+$. Found 202.0966.

3-Amino-6-phenylpyridazine (1e). Yield (136.8 mg, 40%), R_f = 0.72 (EtOAc); mp 134-136 °C; IR (KBr): ν cm^{-1} 3420 (N-H stretch), 3150 (N-H stretch), 1600 (N-H bend); ^{1}H NMR (DMSO-d_6): δ ppm 7.93 (2H, d, *J* = 7.3 Hz, H-2′, H-6′), 7.78 (1H, d, *J* = 9.3 Hz, H-4), 7.34-7.46 (3H, m, H-3′, H-4′, H-5′), 6.86 (1H, d, *J* = 9.3 Hz, H-5), 6.47 (2H, s, NH_2). FAB HRMS (acetone/NBA) calcd. for $C_{10}H_{10}N_3$ 172.0875 $[M+H]^+$. Found 172.0873.



Scheme 1. **Synthesis of iminopyridazine butyronitriles.**

3-Amino-6-(3,5-bistrifluromethylphenyl) pyridazine (1d). Yield (399.1 mg, 65%); R_f = 0.83 (EtOAc); mp 166-168 °C; IR (KBr): ν cm^{-1} 3300 (N-H stretch), 3150 (N-H stretch), 1652 (N-H bend); ^{1}H NMR (DMSO-d_6): δ ppm 8.78 (2H, s, H-2′, H-6′), 8.28 (1H, d, *J* = 12.0 Hz, H-4), 8.26 (1H, s, H-4′), 7.05 (1H, d, *J* = 9.2 Hz, H-5), 6.94 (2H, s, NH_2). FAB HRMS (acetone/NBA) calcd. for $C_{12}H_8N_3F_6$ 308.0622 $[M+H]^+$. Found 308.0623.

3-Amino-6-(1-naphthyl) pyridazine (1f). Yield (216.6 mg, 49%); R_f = 0.72 (EtOAc); mp 153-155 °C; IR (KBr): ν cm^{-1} 3480 (N-H stretch), 3360 (N-H stretch), 1600 (N-H bend); ^{1}H NMR (DMSO-d_6): δ ppm 8.47 (1H, s, H-2′), 8.21 (1H, d, *J* = 9.6 Hz, H-4), 7.93-8.01 (4H, m, H-3′, H-6′, H-7′, H-8′), 7.51-7.56 (2H, m, H-4′, H-5′), 6.91 (1H, d, *J* = 9.6 Hz, H-5), 6.54 (2H, s, NH_2). FAB HRMS (acetone/NBA) calcd. for $C_{14}H_{12}N_3$ 222.1031 $[M+H]^+$. Found 222.1042.

General procedure for the synthesis of 4-(3- aryl-1, 6-dihydro-6-iminopyridazin-1-yl) butyronitrile hydrobromides (2a-2f)

A mixture of 3-amino-6-arylpyridazine (150 mg) and 4-bromobutyronitrile (1.2 eqv.) in DMF (1.0 mL) was heated at 80 ºC for 48 hours. Upon completing the reaction, the reaction mixture was dried over the rotary vacuum evaporator and purified by recrystallization with MeOH and EtOAc.

4-[1,6-Dihydro-3-(4-flurophenyl)-6-iminopyridazin-1-yl]butyronitrile hydrobromide (2a). Yield (131.1 mg, 49%); R_f = 0.77 (MeOH); mp 199-200 °C; IR (KBr): ν cm^{-1} 3440 (NH), 2240 (C≡N), 1660 (C=N); ^{1}H NMR (DMSO-d_6): δ ppm 9.20 (1H, bs, C=NH), 8.40 (1H, d, *J* = 9.6 Hz, H-4), 8.04 (2H, dd, *J* = 5.6, 2.8 Hz, H-3′, H-5′), 7.64 (1H, d, *J* = 9.6 Hz, H-5), 7. 40 (2H, dd (overlapped), J = 8.8 Hz, H-2′, H-6′), 4.37 (2H, t, *J* = 6.8 Hz, $CNC\underline{H}_2CH_2CH_2$), 2.65 (2H, t, *J* = 7.2 Hz, $CNCH_2CH_2C\underline{H}_2$), 2.16 (2H, qn, *J* = 6.8 Hz, $CNCH_2C\underline{H}_2CH_2$). FAB HRMS (Acetone/ NBA) calcd. for $C_{14}H_{14}N_4F$ 257.1202 $[M-Br]^+$. Found 257.1212.

4-[3-(4-Chlorophenyl)-1,6-dihydro-6-iminopyridazin-1-yl]butyronitrile hydrobromide (2b). Yield (74.8 mg, 29%); R_f = 0.37 (MeOH); mp 262-263 °C; IR (KBr): ν cm^{-1} 3450 (NH), 2250 (C≡N), 1653 (C=N); ^{1}H NMR (DMSO-d_6): δ ppm 9.20 (1H, bs, C=NH), 8.43 (1H, d, *J* = 9.6 Hz, H-4), 8.02 (2H, d, *J* = 8.4 Hz, H-3′, H-5′), 7.64-7.67 (3H, m, H-5, H-2′, H-6′), 4.40 (2H, t, *J* = 6.8 Hz, $CNC\underline{H}_2CH_2CH_2$), 2.68 (2H, t, *J* = 7.2 Hz, $CNCH_2CH_2C\underline{H}_2$), 2.18 (2H, qn, *J* = 7.2 Hz, $CNCH_2C\underline{H}_2CH_2$). FAB HRMS (Acetone/NBA) calcd. for $C_{14}H_{14}N_4Cl$ 273.0907 $[M-Br]^+$. Found 273.0907.

4-[1,6-Dihydro-6-imino-3-(3-methoxyphenyl) pyridazin-1-yl]butyronitrile hydrobromide (2c). Yield (104.2 mg, 40%); R_f 0.23 (MeOH); mp 221-222 ºC; IR (KBr): ν cm^{-1} 3350 (NH), 2250 (C≡N), 1650 (C=N); ^{1}H NMR (DMSO-d_6): δ ppm 9.20 (1H, bs, C=NH), 8.45 (1H, d, *J* = 9.6 Hz, H-4), 7.67 (1H, d, *J* = 9.6 Hz, H-5), 7.47-7.58 (3H, m, H-2′, H-4′, H-5′), 7.15 (1H, d, *J* = 8.0 Hz, H-6′), 4.41 (2H, t, *J* = 6.4, $CNC\underline{H}_2CH_2CH_2$), 3.84 (3H, s, OCH_3), 2.68 (2H, t, *J* = 6.8 Hz, $CNCH_2CH_2C\underline{H}_2$), 2.18 (2H, qn, *J* = 6.4 Hz, $CNCH_2C\underline{H}_2CH_2$). FAB HRMS (Acetone/NBA) calcd. for $C_{15}H_{17}N_4O$ 269.1402 $[M-Br]^+$. Found 269.1404.

4-[3-(3,5-Bis(trifluromethylphenyl)-1,6-dihydro-6-iminopyridazin-1-yl] butyronitrile hydrobromide (2d). Yield (64.5 mg, 29%); R_f = 0.24 (MeOH); mp 238-239 °C; IR (KBr): ν cm^{-1} 3440 (NH), 2250 (C≡N); ^{1}H NMR (DMSO-d_6): δ ppm 9.20 (1H, bs, C=NH), 8.68 (1H, d, *J* = 9.6 Hz, H-4), 8.66 (2H, s, H-2′, H-6′), 8.35 (1H, s, H-4′), 7.75 (1H, d, *J* = 9.6 Hz, H-5), 4.48 (2H, t, *J* = 6.4 Hz, $CNC\underline{H}_2CH_2CH_2$), 2.69 (2H, t, *J* = 7.2 Hz, $CNCH_2CH_2C\underline{H}_2$), 2.19 (2H, qn, *J* = 6.4 Hz, $CNCH_2C\underline{H}_2CH_2$). FAB HRMS (Acetone/NBA) calcd. for $C_{16}H_{13}N_4F_6$ 375.1044 $[M-Br]^+$. Found 375.1049.

4-[1,6-Dihydro-6-imino-3-(phenyl)pyridazin-1-yl] butyronitrile hydrobromide (2e). Yield (167.9 mg, 60%); R_f = 0.78 (MeOH); mp 193-194 ºC; IR (KBr): ν cm^{-1} 3440 (NH), 2260 (C≡N), 1660 (C=N); ^{1}H NMR (DMSO-d_6): δ ppm 9.20 (1H, bs, C=NH), 8.42 (1H, d, *J* = 9.2 Hz, H-4), 7.99 (2H, dd, *J* = 8.8, 3.2 Hz, H-2′, H-6′), 7.66 (1H, d, *J* = 9.6 Hz, H-5), 7.56-7.58 (3H, m, H-3′, H-4′, H-5′), 4.40 (2H, t, *J* = 6.8 Hz, $CNC\underline{H}_2CH_2CH_2$), 2.67 (2H, t, *J* = 7.2 Hz, $CNCH_2CH_2C\underline{H}_2$), 2.18 (2H, qn, *J* = 7.2 Hz, $CNCH_2C\underline{H}_2CH_2$). FAB HRMS (Acetone/NBA) calcd. for $C_{14}H_{15}N_4$ 239.1297 $[M-Br]^+$. Found 239.1295.

4-[1,6-Dihydro-6-imino-3-(1-naphthyl) pyridazin-1-yl]butyronitrile hydrobromide (2f). Yield (100.2 mg, 40%); R_f = 0.67 (MeOH); mp 181-183 °C; IR (KBr): ν cm^{-1} 3440 (NH), 2250 (C≡N), 1660 (C=N); ^{1}H NMR (DMSO-d_6): δ ppm 9.20 (1H, bs, C=NH), 7.97-8.13 (4H, m, H-4, H-2′, H-7′, H-8′), 7.58-7.69 (5H, m, H-5, H-3′, H-4′, H-5′, H-6′), 4.39 (2H, t, *J* = 6.8 Hz, $CNC\underline{H}_2CH_2CH_2$), 2. 67 (2H, t, *J* = 7.2 Hz, $CNCH_2CH_2C\underline{H}_2$), 2.17 (2H, qn, *J* = 6.8 Hz, $CNCH_2C\underline{H}_2CH_2$). FAB HRMS (Acetone/NBA) calcd. for $C_{18}H_{17}N_4$ 289.1453 $[M\text{-}Br]^+$. Found 289.1480.

Results and Discussion

In this study, a series of six new 4-(3-aryl-1,6-dihydro-6-iminopyridazin-1-yl)butyronitrile hydrobromides **2a-2f** were synthesized (**Scheme 1**). γ-Aminobutyric acid (GABA) is an agonist and acts as a major inhibitory neurotransmitter in the animal nervous system. The accessory binding site theory of Ariëns suggests that the polar agonists are often transformed into antagonists if hydrophobic rings (usually phenyl rings) are attached to original agonists (Wermuth et al., 1987). Moreover, the bioisosteric replacement of carboxylic moiety by nitrile in the GABA scaffold of gabazine (Fig. 1) exhibited enhanced antagonistic activity in ρ1 receptor (Yamamoto et al., 2012). Those findings justified the synthesis of iminopyridazine butyronitrile analogs taking gabazine as a lead compound, in which various aryl groups modified the 3-position of pyridazine ring, and a carboxylic moiety of GABA part was replaced by nitrile group. The synthesis involved two steps starting from commercially available 3-amino-6-chloropyridazine. The first intermediates 3-amino-6-arylpyridazines **1a-1f** were synthesized in 23-65% yields using the famous Suzuki-Miyaura cross-coupling reaction in the presence of Pd (0) catalyst according to earlier reports (Maes et al., 2000; Guery et al., 2001; Rahman et al., 2012) (**Scheme 1**). Professor Akira Suzuki awarded Nobel Prize in 2010 for this type of Palladium (0) catalyzed reaction. The reactants used in these reactions are stable to the environment and easy to handle. Among the several cross-coupling techniques, relatively mild conditions are required for Suzuki-Miyaura cross-coupling reactions. Maximum (65%) yield was achieved for 3,5-bis (trifluoromethyl)phenyl analog **1d**. Due to the strong electron-withdrawing character of the substituent, the analog **1d** would have the maximum yield. The steric effect might hinder the cross-coupling reaction in 2-trifluromethyphenyl analog as the reaction did not proceed. The final compounds 4-(3-aryl-1,6-dihydro-6-iminopyridazin-1-yl)butyronitrile hydrobromides **2a-2f** were obtained by the N (2)-alkylation of 3-amino-6-arylpyridazines **1a-1f** with 4-bromobuty-ronitrile. In IR spectrum, a broad absorption band at 3440 cm^{-1} and 2240 cm^{-1} appeared for NH and C≡N functional groups, respectively, for compound **2a**. The ^{1}H NMR spectrum, for the analog **2a** displayed a broad singlet at 9.20 ppm for C=NH proton. Two proton doublets at 8.40 ppm (1H, d, *J* = 9.6 Hz) and 7.64 ppm (1H, d, *J* = 9.6 Hz), respectively, appeared for pyridazine protons. A two protons doublet of a doublet at 8.04 ppm (2H, dd, *J* = 5.6, 2.8 Hz) and an overlapped dd at 7. 40 ppm (2H, dd (overlapped), *J* = 8.8 Hz) were found for phenyl protons. The $>CH_2$

protons in different position of alkyl part appeared at 4.37 ppm (2H, t, J = 6.8 Hz), 2.65 ppm (2H, t, J = 7.2 Hz), and 2.16 ppm (2H, qn, J = 6.8 Hz). The $>CH_2$ protons adjacent to the nitrile group appear downfield relative to others due to CN functionality's electron withdrawing nature. High-resolution mass spectrometry (HRMS) is extensively used to determine the molecular mass of unknown compounds with high accuracy. The most intense (100%) peak is the most stable peak, which is known as the base peak in mass spectrometry. All the synthesized compounds described in this paper contain nitrogen atoms. The nitrogen rule states that organic compounds having odd mass indicates to have an odd number of nitrogen atoms in their structure. In contrast, even mass indicates having an even number of nitrogen atoms. All first step compounds **1a-1f** (**Scheme 1**) contain three nitrogen atoms showed even mass numbers as they appeared as $[M+H]^+$ in mass spectra. On the other hand, the second step compounds **2a-2f (Scheme 1)** showed odd mass although they contain four nitrogen atoms as they appeared as $[M-Br]^+$ in mass spectra. In the HRMS, the measured values agreed with the calculated values that confirm the synthesized compound's structures. Further activity study of the synthesized analogs might prove useful for future drug discovery.

Conclusion

In this study, we have synthesized six new 4-(3-aryl-1, 6-dihydro-6-iminopyridazin-1-yl) butyronitrile hydrobromides starting from 3-amino-6-chloropyridazine in two steps. As these types of derivatives act as competitive antagonists in GABA receptors, the results presented in this paper would help future drug development after further activity study.

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