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# Design, Synthesis and Biological Evaluation of Some New Derivatives of Azoles Bearing Pyrrolo [2, 3-d] Pyrimidine Nucleus as Janus Tyrosine Kinase Inhibitors for the Treatment of Auto Immune Disease

**Vikash Srivastava[1], Surya P. Singh[2]**

[1, 2] Magadh University, Department of chemistry, Bidhgaya, Gaya, Bihar-824231 India

[2] Professor, Magadh University, Department of chemistry, Bidhgaya, Gaya, Bihar-824231 India

**Abstract:** ***JAK-associated diseases include autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, juvenile arthritis, type I diabetes, lupus, psoriasis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, autoimmune thyroid disorders. The Janus kinase (JAK) family is one of the recognized families of non-receptor TKs. We revealed a potent and highly discerning inhibitor of JAK3 over JAK1 and -2 based on the substituted structure of 4-chloro-5-iodo-7H-pyrrolo [2, 3-d] pyrimidine. The synthesis of a new series of 1-(1-(tert-butoxycarbonyl) piperidin-4-yl cyclopropane-1-carboxylic acid incorporated with substituted Thaidiazole and Triazole were synthesized, which was reacted with substituted 4-chloro-5-iodo-7H-pyrrolo [2, 3-d] pyrimidine is reported here. A new series of 13 derivatives were synthesized and tested for JAK inhibitory activities. The triazole substituted derivatives 7H-pyrrolo [2, 3-d] pyrimidine compounds (17j-m) showed moderate to high JAK-3 activity against Tofacitinib.***

**Keywords:** Janus Kinase. 4-Chloro-5-Iodo-7H-Pyrrolo [2, 3-d] Pyrimidine. 1-(1-(Tert-butoxycarbonyl) Piperidin-4-yl Cyclopro -pane-1-Carboxylic acid. Thaidiazole. Triazole

## 1. Introduction

Protein kinases (PTKs) are enzymes that direct the biological activity of proteins by phosphorylation of specific amino acids with ATP as the source of phosphate, thus blend up a conformational change from an inactive to an active form of the protein**.** Kinases are improper enzyme activity arising from mutation, over expression, inappropriate regulation, dys-regulation, have been concerned for several diseases, not imitated to cancer, allergies, respiratory disorder but also with inflammatory and other diseases as well. As a result improper enzyme activity triggers a spread of biological cellular responses, regarding cell growth, cell segregation, survival cell death, mitogenesis, cell cycle management and cell quality concerned within the implicit and associated diseases. The Janus kinase (JAK) family is one of the acknowledged families of non-receptor TKs. Thus we are focusing the JAK inhibitory activities of signaling cascade [1-3].

It is composed of four members in mammals, JAK-1, JAK-2, JAK-3 and Tyrosine kinase 2 (Tyk2). These kinases play important roles in cytokine signaling. Upon binding to their receptors, cytokines activate JAK, which in turn phosphorylates the cytokine receptors, thereby creating a binding site for signaling molecules. These molecules are usually members of the signal transducer and activator of transcription (STAT) family that ultimately lead to gene expression. The JAK signaling pathway is activated in many malignancies and inflammatory diseases. Unlike JAK1, JAK2 and Tyk2, whose expression is universal, JAK3 is mainly restricted in hematopoietic cells. Janus kinase inhibitors moreover recognized as JAK inhibitors or jakinibs.

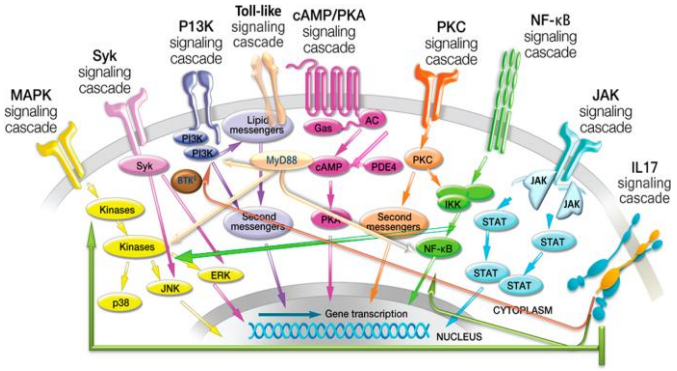



**Figure 1:** Cytokine receptor superfamilies and connected signal transduction pathways. Protein kinases attribute significantly as intermediaries in signal transduction. The complex nature of these signaling pathways leads to redundancies in some cases. Conversely, there are no known compensatory pathways around JAK/STAT. Moreover, many cytokine receptors lack intrinsic kinase activity, instead relying on connected tyrosine kinases, such as the JAKs to transmit signals from the extracellular environment to the nucleus. Therefore, many cytokines and growth factors important for a variety of immune, inflammatory, and hematopoietic functions signal through JAK/STAT

Protein essential for signaling for certain type I and type II cytokines. It interact with the normal gamma chain (γc) of type I cytokine receptors, to illustrate signals from the IL-2

receptor family (e.g. IL-2R, IL-7R, IL-9R and IL-15R), the IL-4 receptor family (e.g. IL-4R and IL-13R), the gp130 receptor family (e.g. IL-6R, IL-11R, LIF-R, OSM-R, cardiotrophin-1 receptor (CT-1R), ciliary neurotrophic factor receptor (CNTF-R), neurotrophin-1 receptor (NNT-1R) and (Leptin-R). It is also considerable for transducing a signal by type I (IFN-α/β) and type II (IFN-γ) interferons, and members of the IL-10 family via type II cytokine receptors [4].

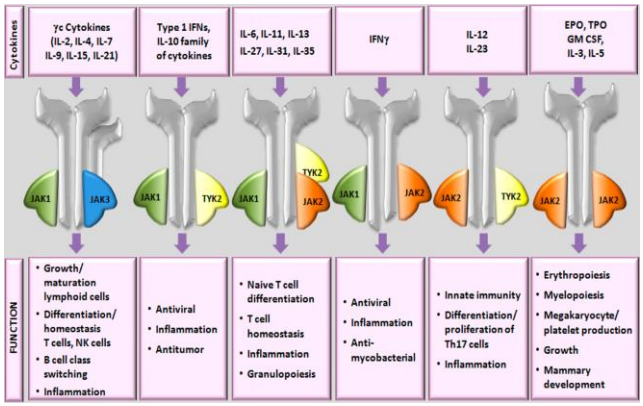
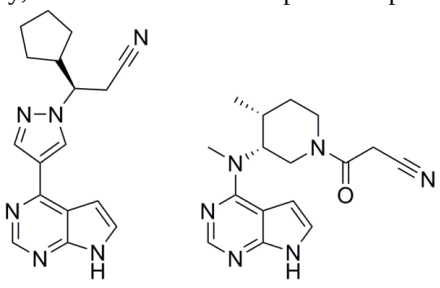



**Figure 2:** Biological significance of signaling through different JAK combinations. Cytokine signaling is mediated by specific JAK and STAT combinations due to preferential binding to the intracellular domains of the individual cytokine receptor chains. For example, JAK3 only associates with the γ-common chain and therefore only mediates IL-2, -4, -7, -9, -15, and -21 signaling, whereas JAK1 plays a broader role in cytokine signaling.

Pfizer Inc. has patented many pyrrolo [2, 3- *d*] pyrimidines as JAK inhibitors in recent years. The pyrrolopyrimidine group of Tofacitinib (**1**) and Ruxolitinib (**2**), which are FDA approved as a JAK1/2 inhibitor and a JAK3 inhibitor respectively, which is a well-known pharmacophore.



Ruxolitinib (**1**)
JAK1 3.2 nM
JAK2 4.1 nM
JAK3 428 nM

Tofacitinib (**2**)
JAK1 3.2 nM
JAK2 4.1 nM
JAK3 1.6 nM

**Figure 4:** FDA-approved JAK inhibitors Ruxolitinib and Tofacitinib. The IC50 values of Ruxolitinib (1) against JAK 1, -2 and -3 are 3.2, 4.1 and 428 nM, respectively, and those of Tofacitinib (2) are 3.2, 4.1 and 1.6 nM,

Although Ruxolitinib (**2**) is a potent JAK1/2 inhibitor, it exhibits low selectivity between JAK1 and -2. The company continued the research on these types of compounds and patented inhibitors that are generally active on JAK1, 2 and 3, and can be useful for the treatment of several pathologies where these enzymes are involved, including immune disorders, inflammation, cancers and neurodegenerative diseases.

The pyrrolo [2, 3-d] pyrimidines are essential chemical scaffolds and have been extensively used in the design of JAKs inhibitors such as Ruxolitinib and Tofacitinib. To establish these structural and practical issues, the enhancement of selective JAK3 inhibitors is significant yet remains demanding. In this study, we intended and synthesized various derivatives of substituted pyrrolo-pyrimidine skeleton for the discovery of selective and novel JAK inhibitors. Here, we report the synthesis of piperidine substituted some new azoles bearing substituted 7H-pyrrolo [2, 3-d] pyrimidine nucleus, as we synthesize 13 derivatives of this new series compound tested for JAK-1 and JAK-2 and JAK-3 inhibitory activity. We therefore replaced the pyrazole with a piperidine substituted azoles (thiadiazole/triazole) group to plan the target molecules without chirality and lead to the discovery of more potent JAK inhibitors. [5-8].

## 2. Materials and Methods

**Experimental section**

The melting points of compounds were determined by open tube capillary method using Digital Melting Point apparatus (model-B-APC-3), in Celsius scale and uncorrected. Purity of the compound was verified by pre-coated TCL plates (E-Merck Kieselgel 60 F254). $^{1}$H NMR, $^{13}$C NMR spectra are recorded on Varian 400 MHz spectrometer using DMSO-d6 as solvent and tetra-methylsilane (TMS) as internal standard. Mass spectra are recorded on Agilent triple quadruple mass spectrometer equipped with turboion spray interface at 375$^{oC}$. All the organic extracts are dried over sodium sulfate after work up. Unless or else mentioned all the solvents and reagents used are of commercial grade.

**Scheme-1, Experimental Procedure:**

**2-(2-bromopyridin-4-yl) acetic acid (2):**

In a round bottom flask diisopropylamine (3.29 g, 32.5 mmol) in tetrahydrofuran (50 mL) at -78$^{o}$C was added drop wise n-BuLi (15.2 mL, 30.52 mmol) under nitrogen. The resulting solution was warm to -30 $^{o}$C, at this temperature stirred for an hour. Compound (**1**) (3.50g, 2.034mmol) in THF (60mL) was added drop wise at -78 $^{o}$C. The reaction mixture was allowed to warm and stirring was continued at -30 $^{o}$C for 2 h. At this temperature dry-ice was added slowly (Effervescence was observed during addition of dry-ice).The reaction mixture was allow to warm at ambient temperature and stir for an hour. To the reaction mixture ice-cold water was added and extracted with EtOAc to remove impurities. The aqueous layer was acidified with 3N HCl and extracted with DCM. Organics were combined washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 1.4g (49%) of the titled compound (**2)** as white solid; $^{1}$H NMR (400 MHz, DMSO-d6) **ð** 12.66 (s, 1H), 8.32 (d, J= 5.04Hz, 1H), 7.59 (s, 1H), 7.36 (d, J= 4.92 Hz, 1H), 3.69 (s, 2H); MS (ESI+) for m\z=215

**2 (pyridin-4-yl) acetic acid hydro bromides (3):**

In a par bottle 2-(2-bromopyridin-4-yl) acetic acid (**2**) (9.0 g, 41.4 mmol) in EtOH (100 mL) was added 50% moist Pd/C (10 mol %) under nitrogen atm. This reaction mixture was hydrogenated at 55 Psi for 4 h. Reaction mixture was filtered

through glass sintered over celite pad and cake was washed three times with EtOH. Filtrate was concentrated under reduced pressure to afford of the5.7g (87%) titled compound as yellow solid compound**3**; $^1$H NMR (400 MHz, DMSO-d6) **ð** 8.92 (d, J= 6.4 Hz, 2H), 8.03 (d, J=6.2 Hz, 2H), 4.05 (s, 2H).

**4- Ethyl 2-(pyridin-4-yl) acetate (4)**
To a stirred solution of compound **3 (**4.3g, 19.8 mmol) in EtOH (20mL) was added ethanolic-HCl (30mL).The resulting reaction mixture was refluxed for 12h. Reaction mixture was concentrated under reduced pressure. The residue was diluted with water, neutralized with solid sodium bicarbonate, and extracted with EtOAc. Organic layer were washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was triturated with 50% EtOAc in hexane to afford 5.7g (87%) of the titled compound as yellow solid compound**4- Ethyl 2-(pyridin-4-yl) acetate (4);** $^1$H NMR (400 MHz, DMSO-d6) **ð** 8.47 (dd, J=5.6, 4.8Hz, 2H), 7.30 (d, J = 5.76 Hz, 2H), 4.00-4.12 (m, 2H), 3.73 (s, 2H), 1.20 (t, J= 6.2Hz, 3H). MS (ESI+) for m\z=166.2

**5-Ethyl 1-(pyridin-4-yl) cyclopropane-1-carboxylate (5)**
To a stirred solution of compound **4** (4.7 g, 26.4 mmol) in dimethylformamide (40mL) was added sodium hydride (1.36 g, 56.9 mmol) at 0 $^o$C. The resulting solution was stirred at ambient temperature for an hour. Reaction mixture was again cooled at 0 $^o$C then added dibromoethane (7.4 mL, 85.5 mmol) dropwise for a period of 15 min. Then reaction mixture was stirred at ambient temperature for 4 h and quenched with ice water, extracted with EtOAc. Organic layer were collected and washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (100-200 mesh size silica gel and 20-30% EtOAc in hexane as eluent) to afford 4.2g (63.56%) title compound as liquid compound **5-Ethyl 1-(pyridin-4-yl) cyclopropane-1-carboxylate** (**5)** as liquid compound**;** $^1$H NMR (400 MHz, DMSO-d6) **ð**8.48-8.50 (m, 2H), 7.33-7.35 (m, 2H), 4.02-4.00 (m, 2H), 1.46-1.57 (m, 2H), 1.25-1.32 (m, 2H), 1.08-1.18 (t, 3H) MS (ESI+) for m\z=192.4

**6-Ethyl 1-(pyridin-4-yl) cyclopropane-1-carboxylate hydrochloride (6)**
To a stirred solution of compound **5** (4.2g, 21.9 mmol) in DCM (30 mL) was cooled at 0 $^o$C. The dry HCl gas passed up to saturation for a period of 2 h. The reaction mixture was concentrated under reduced pressure and the residue was triturated with hexane to afford 4.2g (88%) title compound **6-Ethyl 1-(pyridin-4-yl) cyclopropane-1-carboxylate hydro -chloride** (**6)** as pale yellow solid; $^1$H NMR (400 MHz, DMSO-d6) **ð**8.84-8.85 (d, J=6.56Hz, 2H), 8.02-8.03 (d, J= 5.56Hz, 2H), 4.07-4.12 ((m, 2H), 1.67-1.70 (m, 2H), 1.49-1.52 (m, 2H), 1.11-1.15 (t, 3H) MS (ESI+) for m\z=191.9

**Ethyl-1-(1-piperidin-4-yl) cyclopropane-1-carboxylate hydrochloride (7):** In a parr-vessel compound **6** (2.0g, 8.79 mmol) in ethanol (20mL) was added $PtO_2$ (200 mg, 10moL %) under nitrogen then hydrogenated 55Psi initial pressure at ambient temperature. Completion of reaction was monitored through TLC. Filtered over celite pad and cake was washed with Ethanol. Filtrates were concentrated under reduced pressure to afford 1.6g (78%) of the title compound **Ethyl-1-(1-piperidin-4-yl) cyclopropane-1-carboxylate hydrochlo- ride** (**7)** as white solid compound; $^1$H NMR (400 MHz, DMSO-d6) **ð**9.21 (bs, 1H), 8.91 (bs, 1H), 3.99-4.05 (m, 2H), 3.19-3.22 (d, J=12.04Hz, 2H), 2.70-2.78 (m, 2H), 1.73-1.80 (m, 2H), 1.59-1.71 (m, 2H), 1.14-120 (t, 3H), 1.03-1.06 (t, 2H), 0.78-0.80 (t, 2H).

**Tert-butyl 4-(1-(ethoxy-carbonyl) cyclopropyl piperidine-1-carboxylate (8):**
To a stirred solution of compound **7** (4.5g, 19.2 mol) in DCM (40 mL) was added triethylamine (4.8 g, 47.9 mmmol) at 0 $^o$C followed by addition of di-t-butyl dicarbonate (6.3mL, 28.7mmol) drop-wise. The reaction mixture was stirred at ambient temperature for overnight. Reaction mixture was diluted with water and organic layer separated. Aquous layer was back extracted DCM, washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel (100-200 mesh size, eluent20%EtOAc in hexane) to afford 5.0g (87.73%) **Tert-butyl 4-(1-(ethoxy-carbonyl) cyclo -propyl piperidine-1-carboxylate (8)** as colorless liquid; $^1$H NMR (400 MHz, DMSO-d6) **ð**3.95-4.05 (m, 3H), 2.59 (bs, 2H), 1.44-1.53 (m, 3H), 1.33-1.38 (m, 11H), 1.12-1.02 (t, 2H), 0.80-0.99 (t, 2H), MS (ESI+) for m\z=298.4

**1-(1-(tert-butoxycarbonyl) piperidin-4-yl cyclopropane-1-carboxylic acid (9)**
To a stirred solution of compound (4.0g, 13.4 mmol) in THF: MeOH (1: 1, 30mL) was added 1M NaOH (30 mL) at ambient temperature. The resulting reaction mixture was stirred at same temperature for 96h.The reaction mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with EtOAc to remove the impurities. The aqueous layer was acidified with 1N HCl and extracted with dichloromethane. Organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was triturated with hexane to afford 2.5g (43.9%) of the title compound**1-(1-(tert-butoxycarbonyl) piperidin-4-yl cyclopropane-1-carboxylic acid (9)** as white solid; $^1$H NMR (400 MHz, DMSO-d6) **ð** 12.06 (s, 1H), 3.95-3.97 (d, J = 10.56Hz, 2H), 2.50 (bs, 2H), 1.45-1.53 (t, 3H), 1.31-1.38 (m, 11H), 0.96-0.99 (m, 2H), 0.70-073 (m, 2H); MS (ESI) + for m/z 270.

**Scheme-2, Experimental Procedure:**

**4-chloro-5-phenyl-7-((2-(trimethylsilyl) ethoxymethyl-7H-pyrrolo [2, 3-d] pyrimidine (11):**
A solution of 4-Choro-5-iodo-7H-pyrrolo [2, 3-d] pyrimidine (9.8 g, 35 mmol) in tetrahydrofuran (250mL) was cooled to 0 $^o$C and treated with sodium hydride (60% in oil, 1.54g, 38.5 mmol) in three portions. Reaction mixturewas stirred at same temperature for 1 hour.2-(Trimethyl silyl) ethoxymethyl chloride (6.4g, 38mmol) was added drop-wise and the reaction mixture was warmed to room temperature and allowed to stir for 3h.The reaction mixture was quenched with sat ammonium chloride and added EtOAc. Organic layer was separated and aquous layer was back extrcted with EtOAc. Organic were combined

washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure.The residue was purified through silica gel column chromatography (100-200 mesh size silica gel and 10: 1Hexane/EtOAc) to afford8.0g (20 mmol, 57%) of the title compound**4-chloro-5-phenyl-7-((2-(trimethylsilyl) ethoxymethyl-7H-pyrrolo [2, 3-d] pyrimidine (11)** as white solid: $^1$H NMR (400 MHz, DMSO-d6): 8.69 (s, 1H), 8.14 (s, 1H), 5.60 (s, 2H), 3.51 (t, J=8Hz, 2H), 0.82 (t, J= 8Hz, 2H), 0.10 (s, 9H). MS (ESI+) for m\z=298.26

**General Procedure for the synthesis of suzuki coupling:** To a stirred solution of compound 4-chloro-5-iodo-{ [2-trimethoxysilyl) ] pyrimidine (1mmol) and Aryl bronic acid (1.5mmol) in a mixture of 1, 2-dimethoxy ethane and water (5: 1) was added potassium carbonate (2 mmol) and [1, 1' – bis (diphenyl phosphino) ferrocene dichloropalladium (II) (0.01 mmol).The reaction mixture was degassed and purged with nitrogen.The reaction mixture was heated to rteflux for 18 hours.The reaction mixture was cooled water was added and extracted with EtOAc.Combined organic extract were washed with brine, dried over anhydrous sodim sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (100-200 mesh size silica gel and 20-30% EtOAc in hexane as an eluent to afford as white solid compound (40-80% yield).

**4-chloro-5-phenyl-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3, d] pyrimidine (12a):** Yield (56.23%) as white solid; $^1$H NMR (400 MHz, DMSO-d6) ð 9.49 (s, 1H), 7.41-7.51 (m, 5H), 6.67 (s, 1H), 5.93 (s, 2H), 3.33 (dd, J = 8.2 Hz, 2H), 0.86 (dd, J = 8.0Hz, 2H), -0.08 (s, 9H); MS (ESI+) for m\z=360.93.

**3-(4-chloro-7-{2-(trimethylsilyl) ethoxy] methyl}-7H-Pyrrolo [2, 3-d] pyrimidine-5yl) benzonitrile (12b):** Yield (40.56%) asYellow solid; $^1$H NMR (400 MHz, DMSO-d6) ð 8.75 (s, 1H), 8.13 (s, 1H), 8.00-8.02 (m, 1H), 7.84-7.92 (m, 2H), 7.68 (dd, J = 7.8 Hz, 1H), 5.70 (s, 2H), 3.60 (dd, J = 8.0Hz, 2H), 0.86 (dd, J = 8.0Hz, 2H), -0.08 (s, 9H); MS (ESI+) for m\z=385.2.

**4-chloro-5-(2-methoxyphenyl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidine (12c):** Yield (55.29%) aswhite solid; $^1$H NMR (400 MHz, DMSO-d6) ð 9.49 (s, 1H), 7.99 (m, 1H), 7.49 (m, 1 H), 7.14-7.15 (m, 3 H), 6.67 (s, 1 H), 5.93 (s, 2 H), 3.79 (s, 3 H) 3.33 (dd, J = 8.2 Hz, 2 H), 0.79 (dd, J = 8.0Hz, 2 H), -0.08 (s, 9 H); MS (ESI+) for m\z=390.3.

**(4-chloro-5-(4-chlorophenyl)-7-((2-(trimethylsilyl) ethoxy (methyl)-7H-pyrrolo [2, 3] pyrimidine (12d):** Yield (48.70%) as white solid; $^1$H NMR (400 MHz, DMSO-d6): ð 9.49 (s, 1H), 7.78 (m, 2H), 7.62 (m, 2 H), 6.67 (s, 1H), 5.93 (s, 2H), 3.33 (dd, J = 8.2 Hz, 2H), 0.86 (dd, J=8.0Hz, 2H), -0.08 (s, 9H). MS (ESI+) for m\z=394.4.

**4-chloro-5-(pyridin-2-yl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidine (12e):** Yield (35%) as white solid; $^1$H NMR (400 MHz, DMSO-d6) ð 9.49 (s, 1H), 8.59 (m, 1H), 7.865 (m, 1 H), 7.14-7.15 (m, 3 H), 6.67 (s, 1 H), 5.93 (s, 2 H), 3.79 (s, 3 H) 3.33 (dd, J = 8.2 Hz, 2 H), 0.79 (dd, J = 8.0Hz, 2 H), -0.08 (s, 9 H). MS (ESI+) for m\z=361.2.

**Scheme-3, ExperimentalProcedure;**

**General procedure for synthesis of compound 13 (R1; Me, Phenyl):** To a stirred solution of compound **9** (9.64mmol) in tetrahydrofuran (30mL) was added diisopropylethylamine ( 24.16mmol) followed by addition of EDC.HCl (19.33mmol) and HOBt (4.8mmol).The reactions mixture was stirred at ambient temperature for 30 min and then added R1-Hydrazide (10.34 mmol) and stirred at same temperature for 12h.The reaction mixture was diluted with water and extracted with EtOAc. Combined organics were washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (100-200 mesh size silica gel and 1-2%MeOH/DCM as eluent).

**Tert-butyl4-(1-(2-acetylhydrazine-1-carbonyl) cyclopro-pyl) piperidine-1-carboxylat (13a): (**74%) yield of title compound as foam solid; $^1$H NMR (400MHz, DMSO-d6) ð 9.54 (s, 1H), 9.30 (s, 1H), 3.97-3.94 (d, J=9.6Hz, 2H), 2.60 (bs, 2H), 1.81 (t, J= 5.6 Hz, 3H), 1.68 (t, J= 5.2 Hz, 1H), 1.55 (t, J= 5.2 Hz, 2H), 1.38 (s, 9H), 1.19-1.09 (m, 2H), 0.82-0.81 (d, J=5.24Hz, 2H), 0.63 (s, 2H); MS (ESI) + for m/z 326.

**tert-butyl4-(1-(2-benzoylhydrazine-1-carbonyl) cyclopropyl) piperidine-1-carboxylate (13b); (60.45**%) yield of title compound as Yellow solid compound; $^1$H NMR (400MHz, DMSO-d6) ð 10.19 (s, 1H), 9.54 (s, 1H), 7.88-7.85 (t, 2H), 7.58-7.54 (t, J=5.2Hz, 1H), 7.50-7.46 (t, J=5.76Hz, 2H), 4.00-3.97 (t, J=2.76Hz, 2H), 2.62 (bs, 2H), 1.75-1.69 (t, J=5.76Hz1H), 1.66-1.62 (d, J=12.4Hz, 2H), 1.39 (s, 9H), 1.24-1.15 (m, 2H), 0.89 (t, J=6.2Hz 2H), 0.69-0.68 (d, J=5.4Hz, 2H); MS (ESI) + for m/z 388.4 (M+H) +.

**General procedure for the synthesis of compound 14 (X=S& N, R1: Me, Phenyl):**

To a stirred solution of compound **10** (7.34 mmol) in tetrahydrofuran (24mL) was added Lawesons reagent (29.53 mmol) and resulting reaction mixture was refluxed for 20h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with EtOAc. The combined organic layer were washed with water and sat. Sodium bicarbonate and brine dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (100-200 mesh size silica gel and 1-2%MeOH/DCM as eluent) to afford as foam solid (32.86%).

**tert-butyl4-(1-(5-methyl-1, 3, 4-thiadiazol-2-yl) cyclopro -pyl) piperidine-1-carboxylate (14a) (X=S, R1=Me);** Yield (32.86 %) of the title compound as foam solid; $^1$H NMR (400MHz, DMSO-d6) ð 3.99-3.96 (d, J=10.62Hz, 2H), 2.64 (s, 5H), 1.66-1.64 (m, 3H), 1.36 (s, 9H), 1.27-1.17 (m, 2H), 1.00-0.99 (d, J=3.76Hz, 4 H); MS (ESI) + for m/z 323.8.

**tert-butyl-4-(1-(5-phenyl-1, 3, 4-thiadiazol-2-yl) cyclo-propyl) piperidine-1-carboxylate (14b) (X=S, R1=Ph):** Yield (28.63%) of the title compound as liquid compound; $^1$H NMR (400MHz, DMSO-d6); 7.93-7.90 (m, 2H), 7.54 (t, J=6.8Hz, 3H), 4.01-3.98 (d, J=11Hz, 2H), 3.82-3.78 (t,

J=5.2Hz, 1H), 2.66 (bs, 2H), 1.72-1.63 (m, 3H), 1.36 (s, 9H), 1.38-1.28 (m, 2H), 1.14-1.11 (d, J=11.72Hz, 4H); MS (ESI) + for m/z 386 (M+H) +.

**Tert-butyl 4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclopro -pyl piperidine-1-carboxylate (X=N, R1 = Ph) (14c):** To a stirred solution of compound (0.73g, 2.5 mmol) in acetonitrile (18 mL) was added ethoxy (phenyl) methylene)-azane (07 g, 6.3 mmol). The reaction mixture was stirred for 30 min ambient temperature. Triethylamine (1.3 mL, 10.6 mmol) was added and heated to reflux for 20h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Residue was purified by column chromatography (100-200 mesh size silica gel and 1-2% MeOH / $CH_2Cl_2$) to afford (Yield=54.32%) of the title compound**14**as foam solid; $^1$H NMR (400MHz, DMSO-d6) ð 13.62 (s, 1H), 7.97-7.90 (m, 2H), 7.50-7.30 (m, 2H), 3.97 (s, 2H), 2.63 (bs, 2H), 1.66-1.63 (d, J=12.16Hz, 2H), 1.57-1.47 (m, 2H), 1.37-135 (d, J=10.6Hz, 9H), 1.30-1.23 (d, 2H), 0.96-0.78 (t, 4H); MS (ESI) + for m/z 369 (M+H) +.

**General procedure for de-protection of compound 15 (X=S&N, R1: Me, Phenyl):**
To a stirred solution of compound **14** (0.6g) in dichlo -romethane (5.0mL) was cooled at 0$^o$C and dry gas was purged for 15 min. Upon saturation reaction mixture concentrated under reduced pressure and the residue was triturated with hexane and acetonitrile to afford of the title compound as follows;

**1-(piperidin-4-yl) cyclopropyl)-1, 3, 4-thiadiazole hydrochloride (X=S, R1: Me) (15a):** Yield (72%) of the title compound as off white solid; $^1$H NMR (400MHz, DMSO-d6) ð 8.94 (bs, 1H), 8.46 (bs, 1H), 3.26-3.23 (d, J=12.4Hz, 2H), 2.84-2.75 (m, 3H), 2.66 (s, 3H), 1.82-1.79 (d, J = 10.96 Hz, 2H), 1.69-1.58 (m, 3H), 1.08-0.99 (m, 2H); MS (ESI) + for m/z 224.2 (M+H) +.

**2-phenyl-5-(1-(piperidin-4-yl) cyclopropyl)-1, 3, 4-thiadi-azole hydrochloride (15b) (X=S, R1: Ph);** Yield (52%) of the title compound as off solid compound; $^1$H NMR (400MHz, DMSO-d6) ð 9.05 (bs, 1H), 8.03 (d, J=12.6Hz, 2H), 7.53 (t, J=9.4Hz, 3H). 2.79-2.69 (m, 4H), 1.68 (m, 1H), 1.56-1.51 (m, 4H), 1.08-0.81 (m, 4H); MS (ESI) + for m/z 294.2 (M+H) +.

**4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclopropyl) piperi -dine hydrochloride (X=N, R1: Ph) (15c);:** Yield (69%) of the title compound as yellow solid compound; $^1$H NMR (400MHz, DMSO-d6) ð 9.15-9.13 (d, J=9.44Hz, 1H), 8.60-8.58 (d, J=9.8Hz, 1H), 8.10-8.08 (t, 2H), 7.53-7.46 (m, 3H), 3.25-3.22 (d, J= 12Hz, 2H), 2.83-2.74 (M, 2H), 1.86-1.83 (d, J=12.4Hz, 2H), 1.76-1.58 (m, 3H), 1.08 (brs, 2H), 0.91 (brs, 2H) ); MS (ESI) + for m/z 269 (M+H) +.

**General synthetic procedure for substitution**: To a stirred solution of 4-chloro-5-phenyl-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidine (1.0eq) in DMF was added cesium carbonate (2.5eq) followed by addition of compound (**15a-c)** (X=S &N, R1: -Me, -Phenyl) (1.2 eq). The resulting reaction mixture was heated at 50 $^o$C for 12h.Upon completion; the reaction mixture was diluted with water and extracted with EtOAc. Combined organic extract were washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (100-200- mesh size silica gel and 20-30% EtOAc in hexane) to afford title compound as solid.

**2-methyl-5-(1-(1-(5-phenyl-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-1, 3, 4-thiadiazole (16a):** Yield (40.2%) of the title compound as white solid; $^1$H NMR (400MHz, DMSO-d6) ð 8.27 (s, 1H), 7.46-7.51 (m, 5H), 6.67 (s, 1H), 5.93 (s, 2H), 3.26-3.23 (t, J =12.4 Hz, 2H), 3.03-3.14 (m, 4H), 2.64 (s, 3H), 1.68 (m, 1H), 1.31-1.56 (m, 4H), 0.80-1.04 (m, 4H), 0.79 (dd, J = 8.0, 7.26 Hz, 2H), -0.08 (s, 9H). MS (ESI) + for m/z=547

**3-(4-(4-(1-(5-methyl-1, 3, 4-thiadiazol-2-yl) cyclopro -pyl) piperidin-1-yl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin-5-yl) benzonitrile (16b):** Yield **(**25%) of the title compound as yellow solid; 1H NMR (400MHz, DMSO-d6) ð 8.27 (s, 1 H), 8.02 (d, J=6.76Hz, 1H), 7.85 (d, J=7.56 Hz, 1H), 7.72-7.79 (m, 2H), 6.67 (s, 1H), 5.93 (s, 2H), 3.26-3.23 (t, J =12.4 Hz, 2H), 3.03-3.14 (m, 4 H), 2.64 (s, 3H), 1.68 (m, 1H), 1.31-1.56 (m, 4H), 0.80-1.04 (m, 4H), 0.79 (dd, J = 8.0, 7.84 Hz, 2H), -0.08 (s, 9H). MS (ESI) + for m/z=572

**2-(1-(1-(5-(2-methoxyphenyl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-5-methyl-1, 3, 4-thiadiazole (16c);** Yield (55%) of the title compound as white solid; $^1$H NMR (400MHz, DMSO-d6) ð 8.27 (s, 1H), 7.99 (d, J=5.2Hz, 1H), 7.15-7.49 (m, 3H), 6.67 (s, 1 H), 5.93 (s, 2H), 3.79 (s, 3H), 3.26-3.23 (d, J =12.4 Hz, 2H), 3.03-3.14 (m, 4H), 2.64 (s, 3H), 1.68 (m, 1H), 1.31-1.56 (m, 4H), 0.80-1.04 (m, 4H), 0.79 (dd, J = 8.0, 7.84 Hz, 2H), -0.08 (s, 9 H). MS (ESI) + for m/z=577.5

**2-(1-(1-(5-(4-chlorophenyl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperi -din-4-yl) cyclopropyl)-5-methyl-1, 3, 4-thiadiazole (16d):** Yield (51%) of the title compound as white solid: $^1$H NMR (400MHz, DMSO-d6) ð 8.27 (s, 1H), 7.78 (d, J=9.24Hz, 2H), 7.82 (d, J=8.46Hz, 2H) 6.67 (s, 1H), 5.93 (s, 2H), 3.26-3.23 (t, J =12.4 Hz, 2H), 3.03-3.14 (m, 4H), 2.64 (s, 3H), 1.68 (m, 1H), 1.31-1.56 (m, 4H), 0.80-1.04 (m, 4H), 0.79 (m, J = 8.0Hz, 2H), -0.08 (s, 9 H). MS (ESI) + for m/z=581.25

**2-methyl-5-(1-(1-(5-(pyridin-2-yl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin -4-yl) piperidin-4-yl) cyclopropyl)-1, 3, 4-thiadiazole (16e):** Yield (37.21%) of the title compound as white solid: $^1$H NMR (400MHz, DMSO-d6) ð 8.59 (d, J = 8.05 Hz, 1H), 8.27 (s, 1H), 7.85 (m, 1 H), 7.32-7.40 (m, 2H), 7.08 (s, 1H), 5.93 (s, 2H), 3.23 (t, J =12.4 Hz, 2H), 3.03-3.14 (m, 4 H), 2.64 (s, 3H), 1.68 (m, 1H), 1.31-1.56 (m, 4H), 0.80-1.04 (m, 4H), 0.79 (m, 2H), -0.08 (s, 9H); MS (ESI) + for m/z=548.25.

**2-phenyl-5-(1-(1-(5-phenyl-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-1, 3, 4-thiadiazole (16f):** Yield (40.26%) of the title compound as white solid: $^1$H NMR (300 MHz, DMSO-d6) ð 8.27 (s, 1H), 8.03 (d, J= 9.88Hz, 2H), 7.71-7.53 (m, 8H), 6.67 (s, 1H), 5.93 (s, 2H), 3.33 (t, J= 5.2Hz, 2H), 3.04-3.34 (m, 4H), 1.31-1.68 (m, 5H), 0.79-1.04 (m, 6H), 0.06 (s, 9H); MS (ESI) + for m/z 609.2 (M+H) +.

**3-(4-(4-(1-(5-phenyl-1, 3, 4-thiadiazol-2-yl) cyclopropyl) piperidin-1-yl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin-5-yl) benzonitrile (16g):** Yield (23.59%) of the title compound as white solid; $^1$H NMR (300MHz, DMSO-d6) ð 8.27 (s, 1H), 8.03 (d, J=5.6Hz, 2H), 7.46-7.53 (m, 8H), 6.67 (s, 1H), 5.93 (s, 2H), 3.33 (t, J=6.46Hz, 2H), 3.03-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.79-1.31 (m, 6H), 0.06 (s, 9H); MS (ESI) + for m/z 634 (M+H) +.

**2-(1-(1-(5-(2-methoxyphenyl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-5-phenyl-1, 3, 4-thiadiazole (16h):** Yield (51.29% ) of the title compound as white solid; $^1$H NMR (400MHz, DMSO-d6) ð 8.27 (s, 1H), 7.46-8.03 (m, 9H), 6.67 (s, 1H), 5.93 (s, 2H), 3.33 (t, J=6.46Hz, 2H), 3.03-3.14 (m, 6 H), 1.31-1.68 (m, 5H), 0.79-1.31 (m, 7H), 0.06 (s, 9H); MS (ESI) + for m/z 638 (M+H) +.

**2-phenyl-5-(1-(1-(5-(pyridin-2-yl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-1, 3, 4-thiadiazole (16i):** Yield (26.34%) of the title compound as (white solid); $^1$H NMR (400MHz, DMSO-d6) ð 8.59 (d, J=5.2Hz, 1H), 8.27 (s, 1H), 8.03 (d, J=6.76Hz, 2H), 7.85 (m, 1H), 7.32-7.53 (m, 5H), 6.67 (s, 1H), 5.93 (s, 2H), 3.33 (t, J=6.46Hz, 2H), 3.03-3.14 (m, 6H), 1.31-1.68 (m, 5H), 0.79-1.31 (m, 6H), 0.06 (s, 9H); MS (ESI) + for m/z 609 (M+H) +.

**5-phenyl-4-(4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclopropyl) piperidin-1-yl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin (16j);** Yield (22.38%) of the title compound as white solid; $^1$H NMR (400MHz, DMSO-d6) ð 13.62 (s, 1H), 8.27 (s, 1H), 8.07 (d, J=6.76Hz, 2H), 7.44-7.51 (m, 8H), 6.67 (s, 1H), 5.93 (s, 2H), 3.33 (t, J= 5.2Hz, 2H), 3.04-3.34 (m, 4H), 1.31-1.68 (m, 5H), 0.79-1.04 (m, 6H), 0.06 (s, 9H); MS (ESI) + for m/z 592 (M+H) +.

**3-(4-(4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclopropyl) piperidin-1-yl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidin-5 yl) benzonitrile (16k):** Yield (30.2%) of the title compound as yellow solid; $^1$H NMR (400MHz, DMSO-d6) ð 13.62 (s, 1H), 8.27 (s, 1H), 8.07 (m, 2H), 7.72-8.02 (m, 4H), 7.44-7.50 (m, 3H), 6.67 (s, 1H), 5.93 (s, 2H), 3.33 (t, J=5.4Hz, 2H), 3.04-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.79-1.04 (m, 6H), 0.06 (s, 9H); MS (ESI) + for m/z 617 (M+H) +..

**5-(2-methoxyphenyl)-4-(4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclopropyl) piperidin-1-yl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidine (16l):** Yield (51.65%) of the title compound as white solid; $^1$H NMR (300MHz, DMSO-d6) ð 13.62 (s, 1H), 8.27 (s, 1H), 7.99-8.07 (m, 4H), 7.44-7.50 (m, 3H), 7.15 (d, J=4.76Hz, 2H), 6.67 (s, 1H), 5.93 (s, 2H), 3.79 (s, 3H), 3.33 (t, J=5.4Hz, 2H), 3.04-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.79-1.04 (m, 6H), 0.06 (s, 9H); MS (ESI) + for m/z 622 (M+H) +.

**5-(4-chlorophenyl)-4-(4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclopropyl) piperidin-1-yl)-7-((2-(trimethylsilyl) ethoxy) methyl)-7H-pyrrolo [2, 3-d] pyrimidine (16m);** Yield (32.9%) of the title compound as white solid; $^1$H NMR (300MHz , DMSO-d6) ð 13.62 (s, 1H), 8.27 (s, 1H), 8.07 (d, J=5.76Hz, 2H), 7.78 (d, J=5.2Hz, 2H), 7.62 ((d, J=6.76Hz, 2H) 7.44-7.50 (m, 3H), 6.67 (s, 1H), 5.93 (s, 2H), 3.33 (m, 2H), 3.04-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.79-1.04 (m, 6H), 0.06 (s, 9H); MS (ESI) + for m/z 625 (M+H) +.

**General procedure for synthesis of compound (17a-m):**
To a stirred solution of compound (**16a-m**) (1.85 mmol) in 6N hydrochloric acid (5.0mL) was heated at 50 $^o$C for 6h. Reaction mixture concentrated under reduced pressure and the residue was triturated with hexane and acetonitrile to afford target compound.

**2-methyl-5-(1-(1-(5-phenyl-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-1, 3, 4-thiadiazole (17a):** Yield (60%) of the title compound as white solid; Chemical Formula: $C_{23}H_{24}N_6S$, Anal. Calcd. For; C, 66.32; H, 5.81; N, 20.18; S, 7.70 found: C, 65.32; H, 6.81; N, 21.18; S, 6.70; $^1$H NMR (400 MHz, DMSO-d6) ð 9.60 (bs, 1H), 8.27 (s, 1H), 7.41-7.51 (m, 5H), 6.67 (s, 1H), 3.03-3.14 (m, 4H), 2.64 (s, 3H), 1.68 (m, 1H), 1.31-1.56 (m, 4H), 0.80-1.04 (m, 4H); $^{13}$C NMR (400 MHz, DMSO-d6); 9.4, 19.1, 24.3, 45.2, 51.1, 105.6, 114.5, 123.5, 125.8, 127.5, 128.5, 129.8 142.7, 151.6, 153.8, 168.2; MS (ESI) + for m/z=417.

**3-(4-(4-(1-(5-methyl-1, 3, 4-thiadiazol-2-yl) cyclopropyl) piperidin-1-yl)-7H-pyrrolo [2, 3-d] pyrimidin-5-yl) benzo -nitrile (17b):** Yield (34.5%) of the title compound as off white solid; Chemical Formula; $C_{24}H_{23}N_7S$; Anal. Calcd. For; C, 65.28; H, 5.25; N, 22.21; S, 7.26; Found; C, 65.28; H, 5.25; N, 23.21; S, 6.26C; $^1$HNMR (300MHz, DMSO-d6) ð 9.60 (brs, 1H), 8.27 (s, 1H), 8.02 (dd, J=5.2, 4.76Hz, 1H), 7.72-7.85 (m, 3H), 6.67 (s, 1H), 3.03-3.14 (m, 4H), 2.64 (s, 3H), 1.68 (m, 1H), 1.31-1.56 (m, 4H), 0.80-1.04 (m, 4H), $^{13}$CNMR (300MHz, DMSO-d6); 9.4, 19.1, 24.3, 45.2, 51.1, 105.6, 113.5, 114.5, 118.2, 123.8, 129.2 130.2, 131.8, 132.2, 137.8, 142.7, 151.6, 153.8, 168.2; MS (ESI) + for m/z=442.5

**3] 2-(1-(1-(5-(2-methoxyphenyl)-7H-pyrrolo [2, 3-d] pyrimi -din-4-yl) piperidin-4-yl) cyclopropyl)-5-methyl-1, 3, 4-thia -diazole (17c):** Yield (44.89%) of the title compound as yellow gum); Chemical Formula: $C_{24}H2_6N_6OS$: Anal. Calcd. For;: C, 64.55; H, 5.87; N, 18.82; O, 3.58; S, 7.18; Found: C, 62.55; H, 7.87; N, 17.82; O, 4.58; S, 7.18, $^1$H NMR (300 MHz, DMSO-d6) ð 9.60 (brs, 1H), 8.27 (s, 1H), 7.99 (d, J=5.4Hz, 1H), 7.49 (t, J=6.2Hz, 1H), 7.14-7.15 (m, 2H), 6.67 (s, 1H), 3.79 (s, 3H), 3.03-3.14 (m, 4H), 2.64 (s, 3H), 1.68 (m, 1H), 1.31-1.56 (m, 4H), 0.80-1.04 (m, 4H), $^{13}$C NMR NMR (300 MHz, DMSO-d6) ð 9.4, 19.1, 24.3, 45.2, 51.1, 56.2, 105.6, 114.5, 116, 121.5, 123.6,

125.2, 129.5, 130.1, 142.7, 151.6, 153.8, 157.2, 168.2; MS (ESI) + for m/z=447.2

**2-(1-(1-(5-(4-chlorophenyl)-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-5-methyl-1, 3, 4-thiadiazo -le (17d):** Yield (64.89%) of the title compound as off white solid; **Chemical Formula: $C_{23}H_{23}ClN_6S$;** Anal. Calcd. For; C, 61.25; H, 5.14; Cl, 7.86; N, 18.64; S, 7.11; Found; C, 62.25; H, 6.14; Cl, 6.86; N, 19.63; S, 7.11; $^1$H NMR (300 MHz, DMSO-d6) ð 9.60 (bs, 1H), 8.27 (s, 1H), 7.78 (d, J=5.6Hz, 2H), 7.78 (d, J=4.8Hz, 2H), 6.67 (s, 1H), 3.03-3.14 (m, 4 H), 2.64 (s, 3H), 1.68 (m, 1H), 1.31-1.56 (m, 4H), 0.80-1.04 (m, 4H); $^{13}$C (300 MHz, DMSO-d6) ð 9.4, 19.1, 24.3, 45.2, 51.1, 105.6, 114.5, 123.1, 128.9, 129.3, 134.3, 142.7, 151.6, 153.8, 167, 168.2; MS (ESI) + for m/z=451.6

**2-methyl-5-(1-(1-(5-(pyridin-2-yl)-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-1, 3, 4-thiadia -zole (17e):** Yield (65.89%) of the title compound as off white solid; **Chemical Formula: $C_{22}H_{23}N_7S$;** Anal. Calcd. For; C, 63.29; H, 5.55; N, 23.48; S, 7.68, Found; C, 61.29; H, 7.55; N, 23.48; S, 7.68; 1H NMR (300 MHz, DMSO-d6) ð 9.60 (brs, 1H), 8.59 (d, J = 8.05 Hz, 1 H), 8.27 (s, 1 H), 7.85 (m, 1 H), 7.32-7.40 (m, 2 H), 6.90 (s, 1H), 3.03-3.14 (m, 4H), 2.64 (s, 3H), 1.68 (m, 1H), 1.31-1.56 (m, 4H), 0.80-1.04 (m, 4H); $^{13}$C NMR (300 MHz, DMSO-d6) ð 9.4, 19.1, 24.3, 45.7, 51.1, 108.6, 118.6, 120.6, 123.6, 137.2, 142.7, 149.2, 151.6, 153.8, 154.6, 167.2, 168.2; MS (ESI) + for m/z=418.6

**2-phenyl-5-(1-(1-(5-phenyl-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-1, 3, 4-thiadiazole (17f):** Yield (59.06%) of the title compound as a off white solid; Chemical Formula: $C_{28}H_{26}N_6S$; Anal. Calcd. For; C, 70.27; H, 5.48; N, 17.56; S, 6.70; Found; C, 71.27; H, 4.48; N, 16.56; S, 7.70; $^1$H NMR (400 MHz, DMSO-d6) ð 9.50 (brs, 1H), 8.27 (s, 1H), 8.03 (d, J=5.6 Hz, 2H), 7.46-7.53 (m, 8H), 6.67 (s, 1H), 3.03-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.80-1.08 (m, 4H); $^1$C NMR (400MHz, DMSO-d6) ð 9.4, 24.3, 45.2, 51.1, 105.6, 114.5, 123.8, 125.5, 127.5, 128.3 129.2, 130.9, 133.4, 151.8, 153.8, 167.9, 168.5, 175.2; MS (ESI) + for m/z 479 (M+H) +.

**3-(4-(4-(1-(5-phenyl-1, 3, 4-thiadiazol-2-yl) cyclopropyl) piperidin-1-yl)-7H-pyrrolo [2, 3-d] pyrimidin-5-yl) benzonitrile (17g):** Yield (58.28%) of the title compound as off white solid; Chemical Formula: $C_{29}H_{25}N_7S$; Anal. Calcd. For; C, 69.16; H, 5.00; N, 19.47; S, 6.37; Found; C, 69.16; H, 6.00; N, 18.47; S, 6.37; $^1$H NMR (400MHz, DMSO-d6) ð 9.70 (brs, 1H), 8.27 (s, 1H), 8.03 (t, J=6.5Hz, 3H), 7.85 (m, 2H), 7.53 (m, 3H), 6.67 (s, 1H), 3.03-3.14 (m, 4 H), 1.31-1.68 (m, 5H), 0.80-1.31 (m, 4H); $^{13}$C NMR (400MHz, DMSO-d6) ð 9.4, 24.3, 45.2, 51.1, 105.6 113.2, 114.5, 118.6, 123.8, 128.2, 129.3, 130.5, 132.2, 133.2, 137, 151.8, 153.8, 167.9, 168.2, 175.2; MS (ESI) + for m/z 504 (M+H) +.

**2-(1-(1-(5-(2-methoxyphenyl)-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-5-phenyl-1, 3, 4-thiadiazole (17h):** Yield= (52.12%) of the title comp -ound as white solid; Chemical Formula: $C_{29}H_{28}N_6OS$; Anal. Calcd. For: C, 68.48; H, 5.55; N, 16.52; O, 3.15; S, 6.30; Found; C, 66.48; H, 7.55; N, 17.52; O, 2.15; S, 6.30; $^1$H NMR (400MHz, DMSO-d6) ð 9.70 (brs, 1H), 8.7 (s, 1H), 7.99-8.03 (m, 3H), 7.46-7.53 (m, 4H), 7.15 (dd, J=5.6, 4.8 Hz, 2H) 6.67 (s, 1H), 3.79 (s, 3H), 3.03-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.80-1.08 (m, 4H); $^{13}$C NMR (400MHz, DMSO-d6) ð 9.4, 24.3, 45.2, 51.1, 56.2, 105.6, 114.5, 116.2, 121.2, 123.8, 125.5, 128.2, 129.2, 130.5, 133.5, 151.8, 153.8, 157.3, 167.9, 168.2, 175.2; MS (ESI) + for m/z 508 (M+H) +.

**2-phenyl-5-(1-(1-(5-(pyridin-2-yl)-7H-pyrrolo [2, 3-d] pyrimidin-4-yl) piperidin-4-yl) cyclopropyl)-1, 3, 4-thiadi-azole (17i):** Yield (72.12%) of the title compound as off white solid; Chemical Formula: $C_{27}H_{25}N_7S$; Anal. **Calcd**. For: C, 67.62; H, 5.25; N, 20.44; S, 6.68; Found; C, 66.62; H, 6.25; N, 19.44; S, 7.68; $^1$H NMR (400MHz, DMSO-d6) ð 9.5 (brs, 1H), 8.58 (d, J= 5.20 Hz, 1H), 8.27 (s, 1H), 8.03 (d, J= 5.76 Hz, 2H), 7.85 (t, J= 5.4 Hz, 1H), 7.53 (d, J= 5.2 Hz, 3H), 7.32-7.40 (m, 2H), 6.86 (s, 1H), 3.03-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.80-1.08 (m, 4H); $^{13}$C NMR (400MHz, DMSO-d6) ð 9.4, 24.3, 45.2, 51.1, 108.6, 118.5, 120.5, 123.6, 128.7, 129.2, 130.9, 133.5, 137.5, 149.2, 151.8, 153.8, 154.6 167.9, 168.2, 175.2; MS (ESI) + for m/z 480.2 (M+H) +.

**5-phenyl-4-(4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclopropyl) piperidin-1-yl)-7H-pyrrolo [2, 3-d] pyrimidine (17j):** Yield (65%) of the title compound as off white solid; Chemical Formula: $C_{28}H_{27}N_7$, Anal. **Calcd**. For: C, 72.86; H, 5.90; N, 21.24 Found:; C, 71.86; H, 6.90; N, 21.24; $^1$H NMR (400 MHz, DMSO-d6) ð 11.12 (brs, 1H), 9.6 (brs, 1H), 8.27 (s, 1H), 8.07 (d, J= 7.6Hz, 2H), 7.41-7.51 (m, 7H), 6.67 (s, 1H), 3.04-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.80-1.04 (m, 4H).$^{13}$C NMR (400MHz, DMSO-d6) ð 9.49, 24.0, 45.1, 51.1, 105.1, 114.4, 123.3, 125.5, 127.5, 129.2, 131.1, 132.5, 151.8, 153.8, 157.6, 159.3, 168.7; MS (ESI) + for m/z 462.5 (M+H) +.

**17k] 3-(4-(4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclo-propyl) piperidin-1-yl)-7H-pyrrolo [2, 3-d] pyrimidin-5-yl) benzonitrile (17k);** Yield (70%) of the title compound as aoff white solid; Chemical Formula: $C_{29}H_{26}N_8$; Anal. **Calcd**. For: C, 71.58; H, 5.39; N, 23.03; cal: Found: C, 72.58; H, 5.39; N, 24.03; $^1$H NMR (400 MHz, DMSO-d6) ð 11.12 (brs, 1H), 9.60 (brs, 1H), 8.27 (s, 1H), 8.02-8.07 (m, 3H), 7.79-7.85 (m, 3H), 7.44-7.50 (m, 3H), 6.85 (s, 1H), 3.04-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.80-1.04 (m, 4H); $^{13}$C NMR (400 MHz, DMSO-d6); 9.4, 24.0, 45.7, 51.1, 105.1, 113.1, 114.2, 118.6, 123.8, 127.5, 129.2, 130.2, 131.8, 132.2, 137.1, 151.8, 153.8, 157.6, 159.3, 168.7; MS (ESI) + for m/z 487.6 (M+H) +.

**5-(2-methoxyphenyl)-4-(4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclopropyl) piperidin-1-yl)-7H-pyrrolo [2, 3-d] pyrimi -dine (17l):** Yield (59%) of the title compound as white solid; Chemical Formula: $C_{29}H_{29}N_7O$: Anal. **Calcd**. For: C, 70.85; H, 5.95; N, 19.94; O, 3.25cal: Found: C, 71.85; H, 4.95; N, 19.94; O, 2.25; 10.4; $^1$H NMR (400MHz, DMSO-d6) ð 13.62 (s, 1H), 9.6 (brs, 1H), 8.27 (s, 1H), 7.99-8.07 (m, 3H), 7.44-7.50 (m, 4H), 7.15 (d, J=5.2, 4.8Hz, 2H), 6.87 (s, 1H), 3.79 (s, 3H), 3.04-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.80-1.04 (m, 4H); $^{13}$C NMR (400 MHz, DMSO-d6) ð 9.49, 24.3, 45.1, 51.1, 56.1, 105.1, 114.2, 116.6, 121.5,

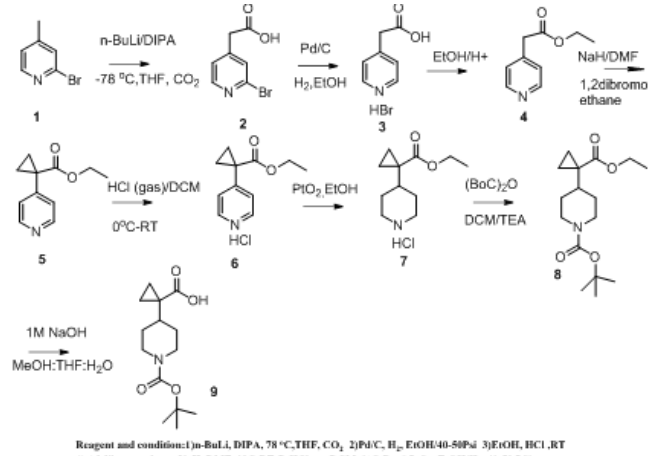
123.8, 125.2, 127.5, 129.2, 130.2, 131.3, 132.5, 151.8, 153.8, 157.6, 159.3, 167.7; MS (ESI) + for m/z 492.6 (M+H) +.

**5-(4-chlorophenyl)-4-(4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclopropyl) piperidin-1-yl)-7H-pyrrolo [2, 3-d] pyrimidine (17m):** Yield (80%) of the title compound as white solid; Chemical Formula: $C_{28}H_{26}ClN_7$, Anal. Calcd. For: C, 67.80; H, 5.28; Cl, 7.15; N, 19.77, Found C, 68.80; H, 4.28; Cl, 6.15; N, 20.77.$^1$H NMR (400MHz, DMSO-d6) ð 13.62 (s, 1H), 9.6 (bs, 1H), 8.27 (s, 1H), 8.07 (d, J= 7.6Hz, 2H), 7.78 (d, J= 5.2Hz, 2H), 7.62 (d, J= 7.6Hz, 2H), 7.44-7.50 (m, 3H), 6.87 (s, 1H), 3.04-3.14 (m, 4H), 1.31-1.68 (m, 5H), 0.80-1.04 (m, 4H); $^{13}$C NMR (400MHz, DMSO-d6) ð 9.49, 24.0, 45.1, 51.1, 105.1, 114.2, 123.5, 127.5,, 129.2, 131.1, 132.2, 134.3, 151.8, 153.8, 157.6, 159.3, 168.7; MS (ESI) + for m/z 496 (M+H) +.

## 3. Results and Discussion

**3.1**: The key intermediate (**9**) in scheme **1,** the starting material 2-Bromo-4-methyl pyridine (**1**) in THF was treated with freshly prepared lithium di-isopropylamide and dry-ice (as source for the $CO_2$) at -78 $^oC$ gave compound (**2**). Des-bromination of compound (**2**) was hydrogenated at 55 psi in presence of palladium on carbon (10mol %) in ethanol to produce a compound (**3**) as salt. Esterification of compound (**3**) on treatment with Ethanolic–HCl to gave compound (**4**). Cyclopropanation of compound (4) was treated 1, 2 dibromorethane with sodium hydride afforded compound (**5**). Which was on reaction with HCl gas in DCM gave compound (**6**). Ring saturation of compound (**6**) in Ethanol was hydrogenated by using $PtO_2$ (platinum oxide) afford corresponding compound (7). Which on protection with boc-anhydride in presence of di-isopropylethylamine in DCM produce compound (**8).** Compound (**8**) on hydrolysis with 1M sodium hydroxide in MeOH: THF: $H_2O$ afford compound (**9**) as a intermediate source for synthesis of azoles [5-12].

**Scheme-1:**




Reagent and condition:1)n-BuLi, DIPA, 78 °C,THF, $CO_2$ 2)Pd/C, $H_2$, EtOH/40-50Psi 3)EtOH, HCl ,RT 4) 1,2dibromoethane, NaH, DMF, 00C-RT 5) HClgas, DCM, 0°C-Rt 6)$PtO_2$, EtOH/$H_2$, 40-50 PSi, rt 7) $(BoC)_2O$, DCM, TEA, 0°C-RT 8) 1M NaOH, MeOH, THF:$H_2O$, rt

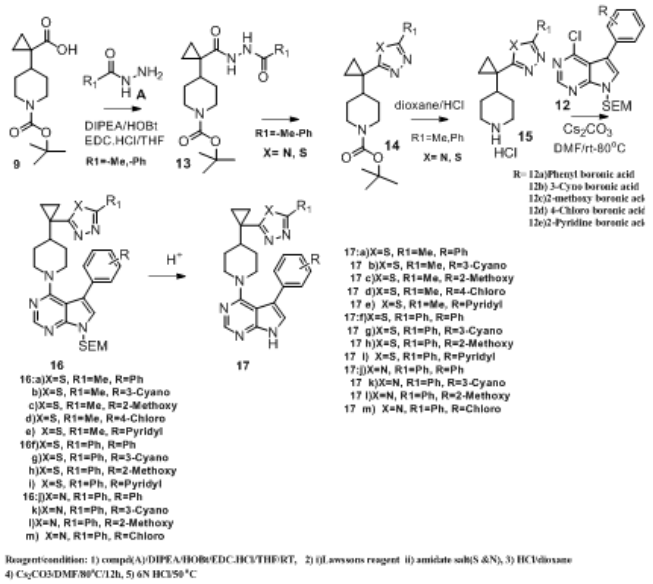
In scheme-**2,** The pyrrole NH moiety of 4-chloro-5-iodo-7H-pyrrolo [2, 3-d] pyrimidine (**10)** was protected with [2-(trimethylsilyl) ethoxy] methyl (SEM) on treatment with sodium hydride in dimethylformamide to afford compound (**11**). Suzuki coupling at 5-postion of (**5**) was reaction with various Ar (BO) $_2$ such as Phenylbronic acid; 4-chlorophenylbronic acid; 3-cycnophenylbronic acid; 2-methoxyphenylbronic acid; 2-pyridinebronic acid in presence of potassium carbonate and Pd (dppf) $Cl_2$ in DME/water at relux condition to yield precursor compounds (**12a-e**).

**Scheme-2**


Reagent/Condition:1)SEM-Cl/NaH/DM/0°C-Rt 2)Ar (BOH) 2 Pd (dppf) Cl2 / $K_2CO_3$/ DME/ water/ 100°C

In scheme **3**, Peptide coupling of compound (**9**) was on treatment with substituted hydrazide (R1= -Me, -Phenyl) in presence of EDC.HCl and 1-Hydroxy benzotriazole followed by addition of diisopropylethylamine gave compound (**13).** Cyclization of compound (**13, R1=-Me, -Ph**) was by using Lawesons reagent yielded to Thaidiazole and on the other hand presence of triethyl amine under heating condition gave corresponding triazole compound (**14, R1=-Me, -Ph & X=N, S**). This was de-protected by using dioxane-HCl to give compound (15). Compound (**15**) on displacement with substituted of compound (**12a-e**) at **4**-position of pyrimidinine was teated with cesium carbonate in dimethyl formamide under heating condition gave compound (**16a-m**). This compounds (**16a-m)** was deprotected by using 6N HCl under heating condition gave a series of new derivatives of compounds (**17a-m**) [**13-19**].

**Scheme-3**




Reagent/condition: 1) compd(A)/DIPEA/HOBt/EDC.HCl/THF/RT, 2) i)Lawssons reagent ii) amidate salt(S &N), 3) HCl/dioxane 4) $Cs_2CO3$/DMF/80°C/12h, 5) 6N HCl/50 °C

### 3.2 Biology

**3.2.1: In vitro enzymatic inhibitory activities:**

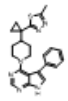
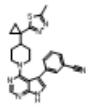
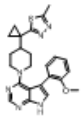
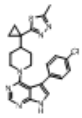
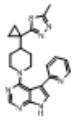
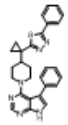
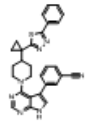
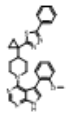
The kinase inhibitory activities of pyrrolo [2, 3-d] pyrimidine **17a-m**, against JAK-1, JAK-2and JAK3 were evaluated by using the Z -LYTETM kinase assay kit (Life Technologies). Tofacitinib, The FDA-approved drug, was used as positive control to validate the screening conditions. The IC50 values against JAK-1 JAK2 and JAK-3kinase displayed by Tofacitinib was 3.2nm, 4.1and 1.6nm the results of the biological assays were summarized in Table;

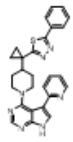
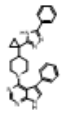
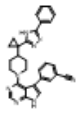
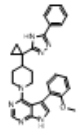
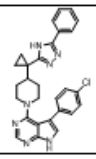
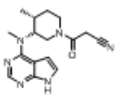
Primarily, all synthesized new derivative compounds were evaluated for their inhibitory activities against JAK kinase family members JAK1, -2 and -3 by screening at

concentrations of 10 and 1μM. **Table 1 (17a-m)** present the percent inhibition of each JAK family member at a 1μM concentration; the IC50 values of selected compounds are denoted in parentheses.

In general, 1) A new synthesized derivatives compounds in entry **table-1** (**17a-m**), Compounds **17c, 17d, 17e, 17f, 17h, 17i and17m**were inactive against all three JAK family members. 2) Compound **17a** and **17b** showed moderate active against JAK-3 and JAK-2 but inactive against JAK-1, compound **17g and 17l** in entry table-1 showed moderate activity against JAK-1, JAK-2 but inactive against JAK-3. Compound **17J-l** showed moderate activity to high activity against JAK-3. Compound **17 k** showed promising activity against JAK-3 but inactive against JAK-1 and JAK-2. Although no appreciable activities or SAR were detected in the series of thadiazole. Potent and inequitable JAK-3 inhibitory activities with clear SAR of the triazole compounds were observed. Most of the current JAK inhibitors contain a nitrile moiety, we attempted to establish various substituent's at the R and R1position, incorporated with thadiazole and triazole groups as well as a C-C coupling of Aryl -group. In the series of thiadiazole-substituted derivatives (**17a-i**), we primarily observed a theatrical increase in JAK1 and -2 and JAK-3 kinase inhibitory activities especially in traazole substituent (**17j-m**), The pattern of inhibitory activities of the series of analogues was as follows: triazole > thadizole with IC50 values. Nitrile-substituted compounds **17b**, **17g** and **17k**, exhibited enhanced inhibition of JAK family members compared with other derivatives. Therefore, triazole - substituted compound **17k** was the most potent and selective inhibitor of JAK-3, with an IC50 value of 8.5, 9.6 and 3.2 selectivity over JAK1, JAK-2 and JAK3, respectively [**19-22**].

**Table 1:** Biological Inhibitory Activity against JAK Family Members, pyrrolopyrimidine based azole

| *Entry* | *Structure* | *Compound Name* | *JAK-1[a] (IC50)[b]* | *JAK-2[a] (IC50)[b]* | *JAK-3[a] (IC50)[b]* |
|---|---|---|---|---|---|
| 17a |  | *2-methyl-5-(1-(1-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)cyclopropyl)-1,3,4-thiadiazole* | *11.3* | *7.6* | *5.6* |
| *17b* |  | *3-(4-(4-(1-(5-methyl-1,3,4-thiadiazol-2-yl)cyclopropyl)piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile* | *9.2* | *0.9* | *7.1* |
| *17c* |  | *2-(1-(1-(5-(2-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)cyclopropyl)-5-methyl-1,3,4-thiadiazole* | 45.4 | 60.4 | -9.4 |
| *17d* |  | *2-(1-(1-(5-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)cyclopropyl)-5-methyl-1,3,4-thiadiazole* | *47.7* | *80.2* | *18.3* |
| *17e* |  | *2-methyl-5-(1-(1-(5-(pyridin-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)cyclopropyl)-1,3,4-thiadiazole* | *81.2* | *93.2* | *15.6* |
| *17f* |  | *2-phenyl-5-(1-(1-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)cyclopropyl)-1,3,4-thiadiazole* | 53.6 | 60.4 | 24.0 |
| *17g* |  | *3-(4-(4-(1-(5-phenyl-1,3,4-thiadiazol-2-yl)cyclopropyl)piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile* | *9.8* | *10.8* | *6.4* |
| *17h* |  | *2-(1-(1-(5-(2-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)cyclopropyl)-5-phenyl-1,3,4-thiadiazole* | 53.6 | 12.0 | 60.4 |

| | | | | | |
|---|---|---|---|---|---|
| *17i* |  | *2-phenyl-5-(1-(1-(5-(pyridin-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)cyclopropyl)-1,3,4-thiadiazole* | **20.2** | **19.0** | **25.4** |
| *17j* |  | *5-phenyl-4-(4-(1-(5-phenyl-4H-1,2,4-triazol-3-yl)cyclopropyl)piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine* | *10.5* | *11.6* | *5.6* |
| *17k* |  | *3-(4-(4-(1-(5-phenyl-4H-1,2,4-triazol-3-yl)cyclopropyl)piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile* | *8.5* | *9.6* | *3.2* |
| *17l* |  | *5-(2-methoxyphenyl)-4-(4-(1-(5-phenyl-4H-1,2,4-triazol-3-yl)cyclopropyl)piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine* | **10.3** | **9.2** | **6.6** |
| *17m* |  | *5-(4-chlorophenyl)-4-(4-(1-(5-phenyl-4H-1,2,4-triazol-3-yl)cyclopropyl)piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine* | **11.7** | **10.8** | **5.1** |
| *Standard* |  | Tofacitinib | **3.2nM** | **4.1nM** | **1.6nM** |

**3.2.2** Promega's Kinase-GloTM Luminescent Kinase Assay is a homogeneous non-radioactive technique for determining the activity of purified kinases by quantifying the amount of ATP remaining in solution following a kinase reaction. The assay method involves accumulation of a single reagent (Kinase-Glo_ Reagent) unswervingly to a completed kinase reaction. This addition results in the creation of a luminescent signal correlated with the amount of ATP present and inversely proportional to the amount of kinase activity. The entire compounds were tested using an assay developed with TF-1 (1, 2) cells (CRL-2003 from ATCC) which proliferatein rejoinder to GM-CSF, IL-3 and IL-4. IL-3 (Human recombinant Sigma #I 1646) or IL-4 (Human recombinant. Sigma #I 4269) at 1 nM was used to arouse the cells. Proliferation of the TF-1 cells was used to assess the responses during JAK2 (IL-3) or JAK3 (IL-4) and the inhibition of such response by unambiguous compounds. Five replicates per compound were seeded at a concentration of 5000 cells/well in a 100 ll volume. Five different concentrations of experimental compounds (5 replicates each) were used to determine their EC50. After 4 days of incubation, cell proliferation was measured during the last 18 h of incubation, using an ELISA (BrdU, chemiluminescence) kit (Roche Diagnostics, Indianapolis, IN). The relative luminescence units (RLU) were measured using a Packard Fusion instrument (Perkin Elmer). RLUwere used to calculate EC50s (Prism4 software).

CP-690, 550 (Tofacitinib), reported to possess 20: 1 selectivity favoring JAK3 over JAK2, showed virtually no selectivity in a separate Kinase ProfilerTM Assays (radiometric filter binding assays) run by Upstate Cell Signaling Solutions (JAK3 IC50 = 5 nM, JAK2 IC50 = 6 nM) [**23**].

**Table 3:** Inhibition of proliferation of TF-1 cells, induced by either IL-3 (for JAK2 activation) or IL-4 (for JAK3 activation), by pyrrolo-pyrimidine analogs.

| Compound | Compound Inhibition of IL-4 induced TF-1 cell proliferation $IC_{50}$ | Inhibition of IL-3 induced TF-1 cell proliferation $IC_{50}$ (nM) |
|---|---|---|
| CP690-550 | 80[b] | 800[b] |
| 17b | 300 | 600 |
| 17g | 345 | 672 |
| 17j | 1200 | 800 |
| 17k | 88 | 700 |
| 17l | 95 | 750 |

**SD for TF-1 cellular assay were typically ±25% of the mean or less. [b] Mean, n > 10.**

## 4. Conclusion

Our results for the synthesis of new derivatives based on the triazole structure and specially 3-(4-(4-(1-(5-phenyl-4H-1, 2, 4-triazol-3-yl) cyclopropyl) piperidin-1-yl)-7H-pyrrolo [2, 3-d] pyrimidin-5-yl) benzonitrile have revealed potent and highly selective JAK3 inhibitors. According various substituted groups at the R position, benzonitrile -substituted compound 17k more potent and selective inhibitor of JAK-3, with an IC50 value of 8.5, 9.6 and 3.2 selectivity over JAK1and JAK-2, respectively

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