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Synthesis of Pyrroles and Condensed Pyrroles as Anti-Inflammatory Agents with Multiple Activities and Their Molecular Docking Study

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Abstract

We herein disclose a series of novel pyrrole derivatives as well as fused pyrrolopyridines 6a,b and 7a,b, pyrrolopyrazoles 8a, b, pyrrolo[2,3-d]pyrimidine derivatives 10a-d, 12a,b, 14a,b, 18a,b, 20a,b, 21a,b, 22a,b, 23a,b, 24a,b, 31a,b, 36a,b, 40a,b, pyrrolo[1,2,6]thiadiazine derivatives 19a,b, pyrrolotriazolopyrimidines 25a,b, 26a,b, 27a,b and 28a,b, pyrrolo[2,3-d][1,2,3]triazine derivatives 32a,b and pyrrolo[2,3-d][1,3]oxazine derivatives 39a,b as novel compounds. All compounds were evaluated for their anti-inflammatory, analgesic (compared to the reference drug Indomethacin) and antimicrobial activities (compared to the reference drug Ampicillin and Fluconazole). Compounds 4d, 5b-d, 6a,b, 9c,d, 10d, 12ab, 13b, 19a,b, 21b, 23b, 31a,b, 38b and 40a were found to be the most active anti-inflammatory drugs exhibiting potency ranging from 1 - 1.01 compared to the reference drug indomethacin. In addition to docking study of these highly active twenty compounds against the active site of cyclooxygenase-2 enzyme (COX-2), among the tested compounds, compounds 5d, 9d, 11b, 12a, 13b and 32a showed multiple activities; anti-inflammatory, analgesic and anti-bacterial activities.

Keywords

Anti-Inflammatory Activity, Pyrrole, Pyrrolo[2,3-d]Pyrimidine, Molecular Modeling

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1. Introduction

Nitrogen heterocycles are of special interest as they constitute an important class of natural and non-natural products as they occupy a key position in the area of drugs and pharmaceuticals [1] [2]. Pyrroles have drawn considerable attention due to their synthetic importance and useful biological activities that are extensively used in drug discovery [3]. Pyrrole derivatives exhibited a vital role in many pharmacological activities including anti-inflammatory [4]-[13], anti-microbial [14]-[19], anti-fungal [20]-[22], antiviral [23]-[25] and anti-cancer [26]-[28] activities.

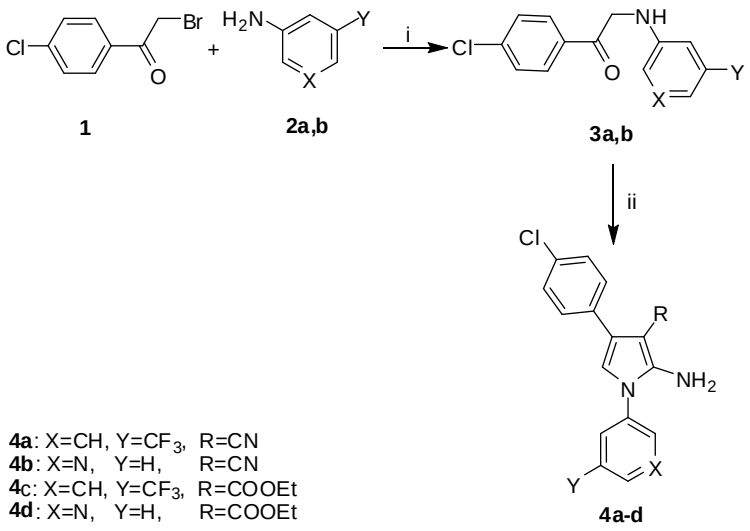
It is well known that the anti-inflammatory activity is due to the ability to inhibit the cyclooxygenase (COX) activity of prostaglandin H synthase, an enzyme which mediates the production of prostanoids (including prostaglandins, prostacyclins and thromboxanes) from arachidonic acid. Prostaglandins act as mediators in the process of inflammation, thus the discovery of COX-2 specific inhibitors (Coxibs), which their pharmacological properties are correlated to their ability to decrease the COX-2 dependent prostanoid biosynthesis, providing a rational for the development of drug devoid of GIT disorders while retaining clinical efficacy as anti-inflammatory agent [29]. The recent market withdrawal of some coxibs such as rofecoxibs (Vioxx®) and valdecoxib (Bextra®) due to their adverse cardiovascular side effects [30] clearly delineates the need to explore and evaluate alternative templates with COX-2 inhibitory activity.

Therefore, our aim was to design derivatives of existing clinically used NSAIDs, such as Tolmetin and Ketorolac [31] [32] which are well known pyrrole derivatives acting as anti-inflammatory drugs. In the light of these facts, this paper deals with the synthesis of novel pyrrole and condensed pyrrole derivatives and evaluates them for their anti-inflammatory activity. Furthermore, the extent of the pharmacological effects of pyrrole derivatives is reported to depend on the active groups which are attached to it, as several scientists have elucidated that in pyrrole system positions 2 and 3, it can be suitably modified by the introduction of groups [28], aromatic [19] [25] or heterocyclic moieties to show excellent pharmacological results [12].

2. Results and Discussion

2.1. Chemistry

Reaction of 4-chlorophenacyl bromide **1** either with 3-trifluoromethyl aniline **2a** in refluxing ethanol or by stirring with 3-amino pyridine **2b** in diethyl ether afforded 2-(substituted amino)-1-(4-chlorophenyl)ethanones **3a,b**; respectively which upon stirring with the active methylene bearing carbonitriles namely; malononitrile and ethyl cyanoacetate in sodium ethoxide afforded 3-substituted-2-amino-4-(4-chlorophenyl)-1-(substitutedaryl)-1H-pyrroles **4a-d** which were utilized as building units for novel substituted pyrrole compounds (**Scheme 1**).

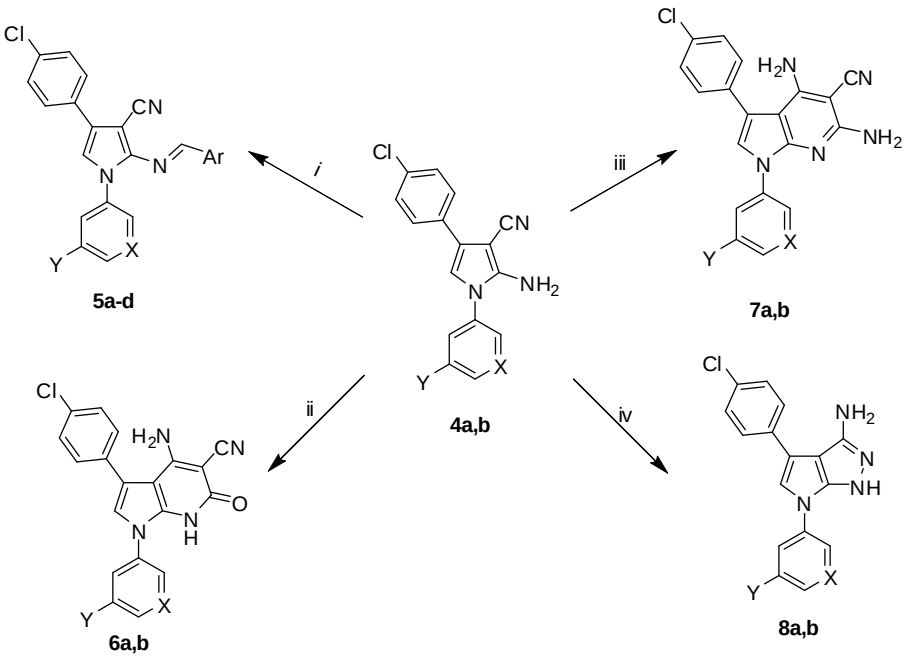


Scheme 1. Synthetic pathways for compounds **3a,b** and **4a-d**.

Furthermore, the *o*-aminonitrile derivatives **4a,b** were condensed with the appropriate aromatic aldehyde namely; benzaldehyde and 2,4-dichlorobenzaldehyde in absolute ethanolto afford the corresponding benzylidenimino derivatives **5a-d** (Scheme 2). Moreover, reaction of compounds **4a,b** either with ethyl cyanoacetate or malononitrile in refluxing ethanol yielded 6-oxopyrrolo[2,3-b]pyridines **6a,b** and 4,6-diamino-pyrrolo[2,3-b]pyridine derivatives **7a,b**; respectively. Additionally, cyclization of compounds **4a,b** with hydroxylamine hydrochloride in boiling sodium ethoxide afforded the aminopyrazole derivatives **8a,b**.

Furthermore, compounds **4a,b** were reacted with urea/thiourea in sodium ethoxide to give the target compounds **9a-d** (Scheme 3), which were cyclized upon refluxing in pyridine to afford the pyrrolopyrimidine derivatives **10a-d** which can also be obtained through refluxing of the *o*-aminonitrile derivatives **4a,b** with urea/thiourea in a mixture of glacial acetic acid and concentrated hydrochloric acid (3:1). Furthermore, the target phenylthioureaderivatives **11a,b** was obtained via refluxing of compounds **4a,b** with phenyl isothiocyanate in absolute ethanol. Also, refluxing of compounds **11a,b** in pyridine afforded the cyclized compounds 4-imino-pyrrolopyrimidine-2-thiones **12a,b** which were also prepared directly via refluxing of compounds **4a,b** with phenyl isothiocyanate in dry pyridine.

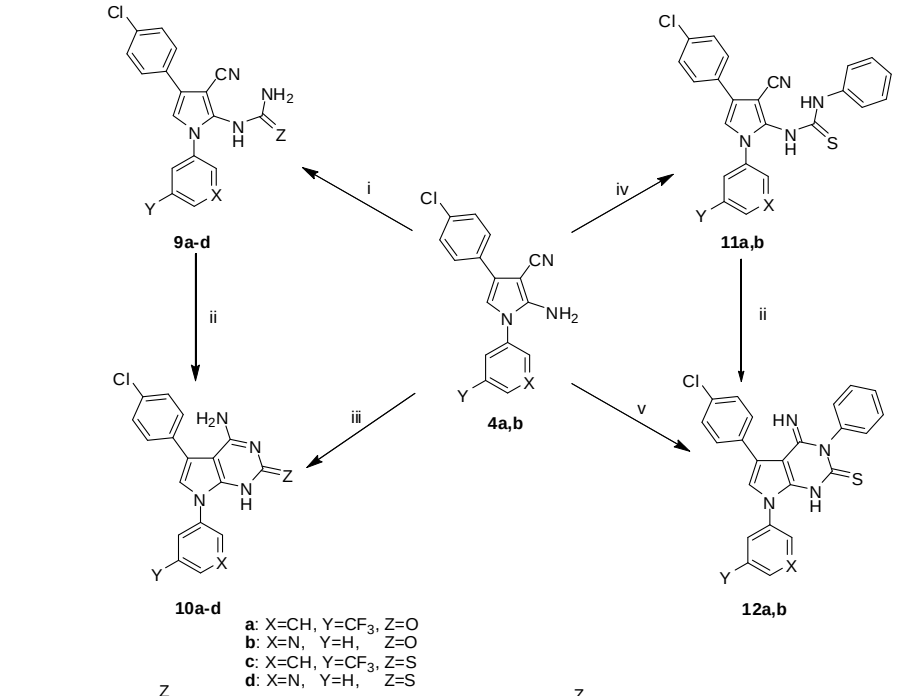
Moreover, our goal was directed to synthesize various substituted pyrrole-3-carbonitrile derivatives bearing different substituted imino side chains in position two of pyrrole (Scheme 4). Therefore, refluxing of compounds **4a,b** in a mixture of triethyl orthoformate and acetic anhydride furnished compounds **13a,b** with a replaceable ethoxymethyleneimino function which were cyclized upon reaction with ammonia in refluxing methanol via elimination of an ethanol moiety to yield 4-aminopyrrolopyrimidine derivatives **14a,b** which were also obtained directly through refluxing of compounds **4a,b** with formamide. On the other hand, stirring of compounds **13a,b** with dimethylamine in absolute ethanol afforded N,N-dimethyl formimidamide derivatives **15a,b** which was also synthesized directly via refluxing compounds **4a,b** with dimethylformamide/dimethylacetal in xylene. Moreover, acylation of compounds **4a,b** was accomplished through refluxing of compounds **4a,b** with *p*-toluene sulphonyl chloride in toluene to afford 4-methylbenzenesulfonamides **16a,b** via elimination of a hydrochloride molecule.



a: X=CH, Y=CF_3, Ar=C_6H_5
b: X=N, Y=H, Ar=C_6H_5
c: X=CH, Y=CF_3, Ar=2,4-$(Cl)_2C_6H_3$
d: X=N, Y=H, Ar=2,4-$(Cl)_2C_6H_3$

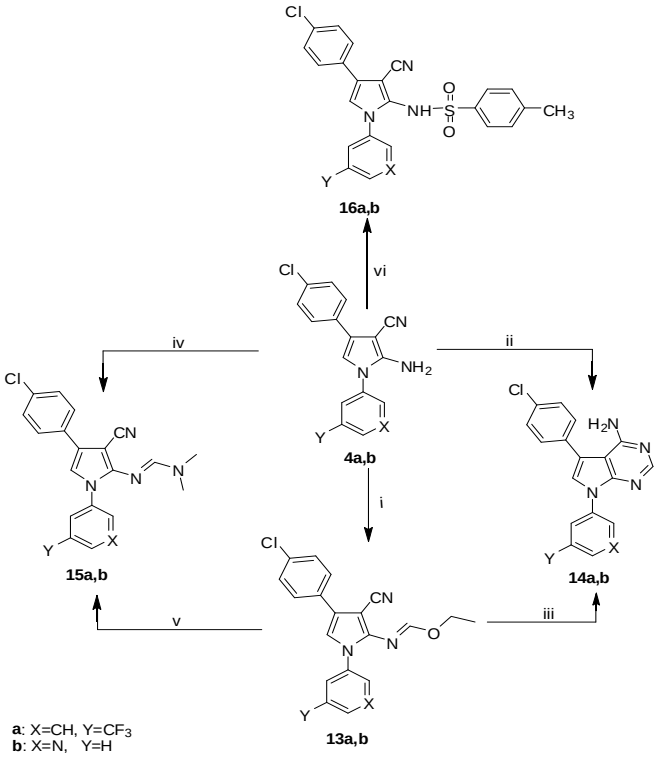
Reagents & conditions: (i) ArCHO /EtOH / reflux; (ii) $CNCH_2COOEt$ / EtOH / reflux; (iii) $CNCH_2CN$ / EtOH / reflux; (iv) $NH_2OH.HCl$ / NaOEt / reflux

Scheme 2. Synthetic pathways for compounds **5a-d**, **6a,b**, **7a,b** and **8a,b**.



Reagents: (i) $H_2N-\overset{\overset{Z}{\|}}{C}-NH_2$/ NaOEt / reflux; (ii) pyridine /reflux; (iii) $H_2N-\overset{\overset{Z}{\|}}{C}-NH_2$/ gl.HOAc / HCl / reflux; (iv) C_6H_5NCS / EtOH / reflux; v) C_6H_5NCS / pyridine / reflux

Scheme 3. Synthetic pathways for compounds **9a-d**, **10a-d**, **11a,b** and **12a,b**.

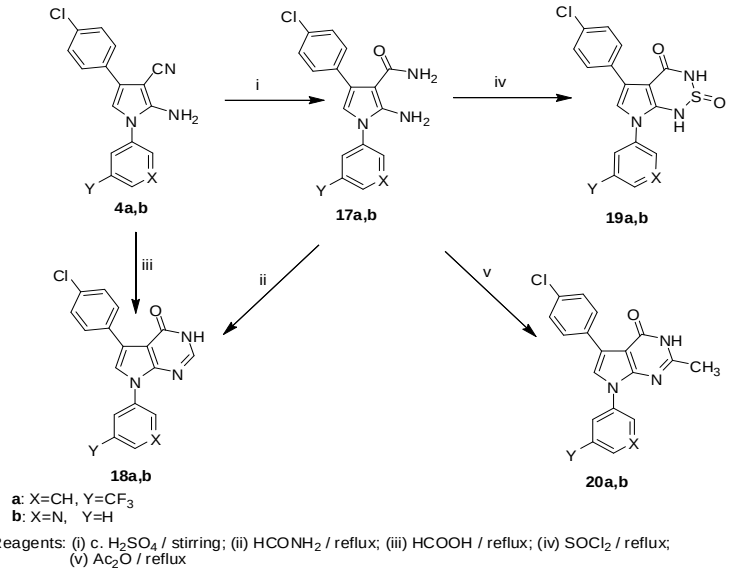


Reagents: (i) TEOF /AC_2O / reflux; (ii) $HCONH_2$ / reflux; (iii) NH_3 / CH_3OH / reflux; (iv) DMF / DMA / xylene / reflux; (v) $HN(CH_3)_2$ / EtOH / stirring; (vi) *p*-toluene sulphonyl chloride / toluene / reflux

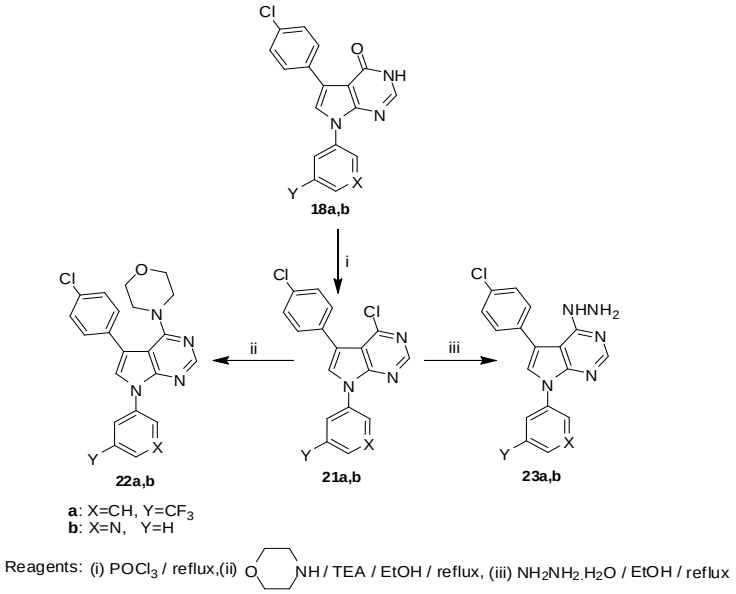
Scheme 4. Synthetic pathways for compounds **13a,b**, **14a,b**, **15a,b** and **16a,b**.

Also, partial hydrolysis of compounds **4a,b** was accomplishedby stirring at room temperature with concentrated sulfuric acid to afford substituted-2-aminopyrrol-3-carboxamides **17a,b** (**Scheme 5**), which undergo cyclization into pyrrolo[2,3-d]pyrimidin-4-ones **18a,b**, pyrrolo[3,2-d]1,2,6-thiadiazine-2,4-diones **19a,b** and 2-methyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-ones **20a,b** upon their refluxing with formamide, thionyl chloride and excess acetic anhydride; respectively. However, the target compounds **18a,b** was also obtained directly by refluxing the *o*-aminonitrile derivatives **4a,b** with formic acid.

Moreover, chlorination of pyrrolopyrimidin-4-one derivatives **18a,b** with excess phosphorus oxychloride followed by alkalinization to pH 10 using sodium bicarbonate furnished 4-chloropyrrolo[2,3-d]pyrimidines **21a,b** (**Scheme 6**). However, the chlorinated compounds **21a,b** were reacted with morpholine in ethanol under reflux in presence of a catalytic amount of triethylamine to furnish the 4-morpholino-pyrrolo[2,3-d]pyrimidines **22a,b**. Furthermore, hydrazinolysis of chloro derivatives **21a,b** was carried out by refluxing with hydrazine hydrate 98% in ethanol in presence of triethylamine as a catalyst to afford 4-hydrazinyl-7H-pyrrolo[2,3-d]pyrimidines **23a,b**.



Scheme 5. Synthetic pathways for compounds **17a,b**, **18a,b**, **19a,b** and **20a,b**.

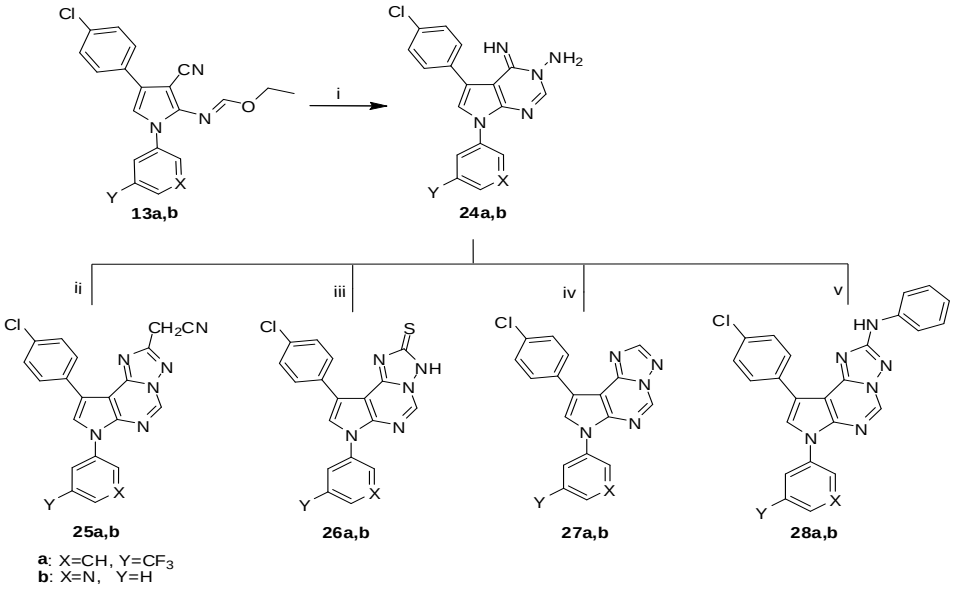


Scheme 6. Synthetic pathways for compounds **21a,b**, **22a,b** and **23a,b**.

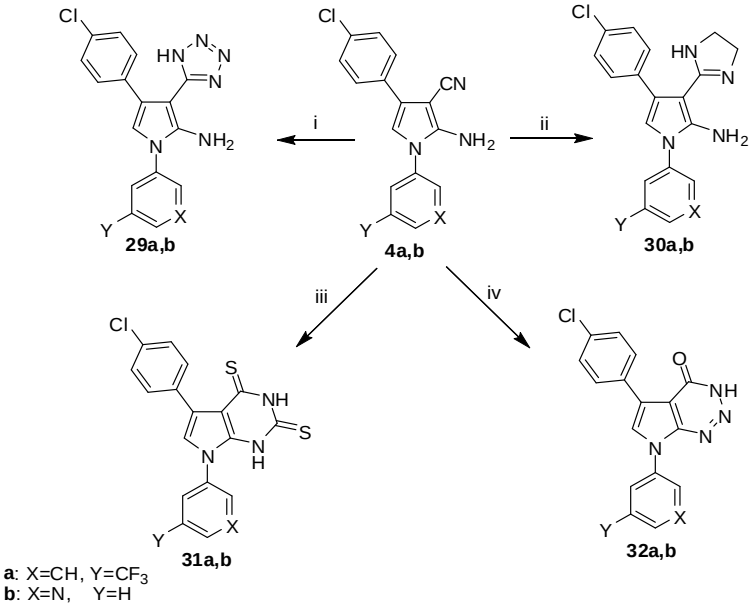
Furthermore, stirring of compounds **13a,b** with hydrazine hydrate 98% in absolute ethanol afforded 4-imino-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidines **24a,b** (**Scheme 7**) which were used as good starting materials for preparation of several pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives. Thus, compounds **24a,b** were reacted with ethyl cyanoacetate in absolute ethanol containing few drops of glacial acetic acid to yield the cyanomethyl triazolopyrimidine derivatives **25a,b**. While, refluxing of compounds **24a,b** with carbon disulphide in absolute ethanol containing potassium hydroxide yielded the corresponding triazolopyrimidine-2-thione derivatives **26a,b**. Moreover, the reaction of the precursors **24a,b** with triethyl orthoformate in absolute ethanol gave the unsubstituted triazolopyrimidine compounds **27a,b**. While, upon refluxing of **24a,b** with phenyl isothiocyanate in absolute ethanol in presence of a catalytic amount of triethylamine afforded the phenyl amine substituted triazolopyrimidine derivatives **28a,b**.

Heating of the *o*-aminonitrile derivatives **4a,b** with sodium azide in presence of ammonium chloride in dimethylformamide as a solvent to furnish 2-aminopyrrol-3-tetrazole derivatives **29a,b** (**Scheme 8**). However, heating compounds **4a,b** with ethylene diamine in the presence of carbon disulphide afforded the target compounds 2-aminopyrrol-3-imidazole derivatives **30a,b**. Also, the *o*-aminonitrile derivatives **4a,b** were refluxed with carbon disulphide in dry pyridine to yield the pyrrolopyrimidine-2,4-dithiones **31a,b**. Besides, pyrrolo[2,3-d][1,2,3]triazin-4-ones **32a,b** were obtained via stirring of compounds **4a,b** with sodium nitrite solution in a mixture of glacial acetic acid and concentrated hydrochloric acid at 0˚C - 5˚C. The reaction mechanism is suggested to proceed first through partial hydrolysis of the cyano function to afford the corresponding *o*-aminocarboxamide derivatives that undergo subsequent diazotization then coupling with amino function of the carboxamide to yield the target 4-oxotriazine derivatives **32a** & **32b**.

This work was extended to shed more light on the activity and synthetic potential of the amino and carboxylate groups in compounds **4c,d** (**Scheme 9**). Thus, compounds **4c,d** reacted with hydrazine hydrate in absolute ethanol to afford the corresponding acid hydrazide derivatives **33a,b**. However, acetylation of amino group in compounds **4c,d** with acetic anhydride afforded the target acetamido derivatives **34a,b**. However, the synthesis of different hydrazone derivatives through the condensation of hydrazine compounds with monosaccharide is well documented in the literature [33]-[35]. Therefore, this information prompted us to explore the effect of glucose hydrazone derivatives **35a,b** whichwere synthesized through the condensation of the hydrazide derivatives **33a,b** with glucose in absolute ethanol. Additionally, the reaction of *o*-acetamidocarboxylate derivatives **34a,b** were refluxed with excess hydrazine hydrate in ethanol to afford the target substituted pyrrolopyrimidinone derivatives **36a,b**. The reaction mechanism is suggested to proceed first through formation of the hydrazone derivatives followed by tautomerism then intramolecular cyclization via elimination of an ethanol molecule.



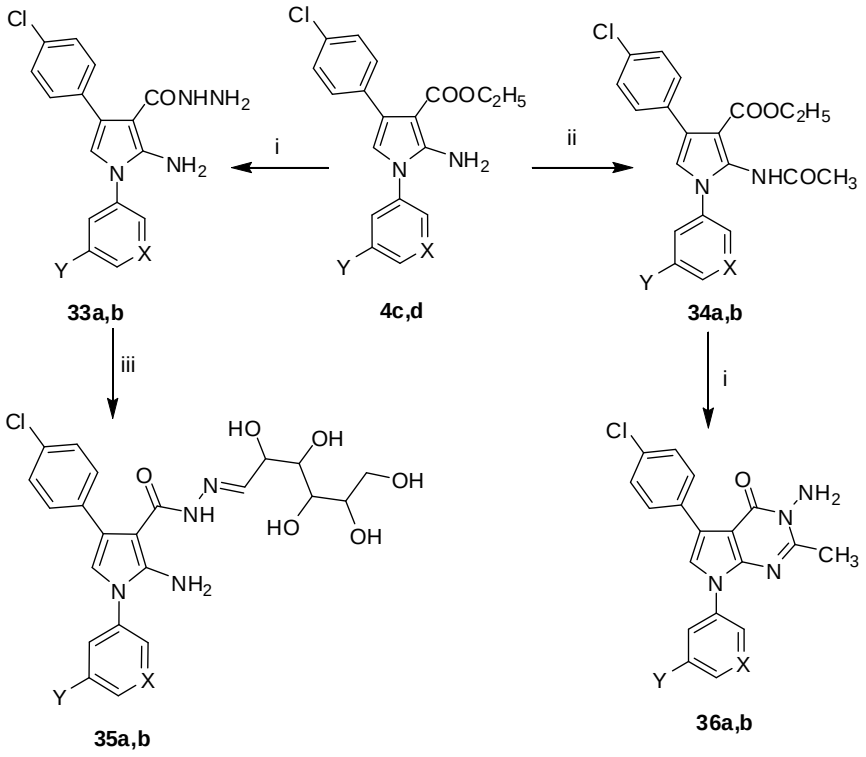
Scheme 7. Synthetic pathways for compounds **24a,b**, **25a,b**, **26a,b**, **27a,b** and **28a,b**.



a: X=CH, Y=CF_3
b: X=N, Y=H

Reagents: (i) NaN_3 / NH_4Cl / DMF/ reflux; (ii) $NH_2(CH_2)_2NH_2$ / CS_2 /reflux; (iii) CS_2 / pyridine / reflux; (iv) $NaNO_2$ / gl.HOAc/HCl / stirring / 0-5 ^0C

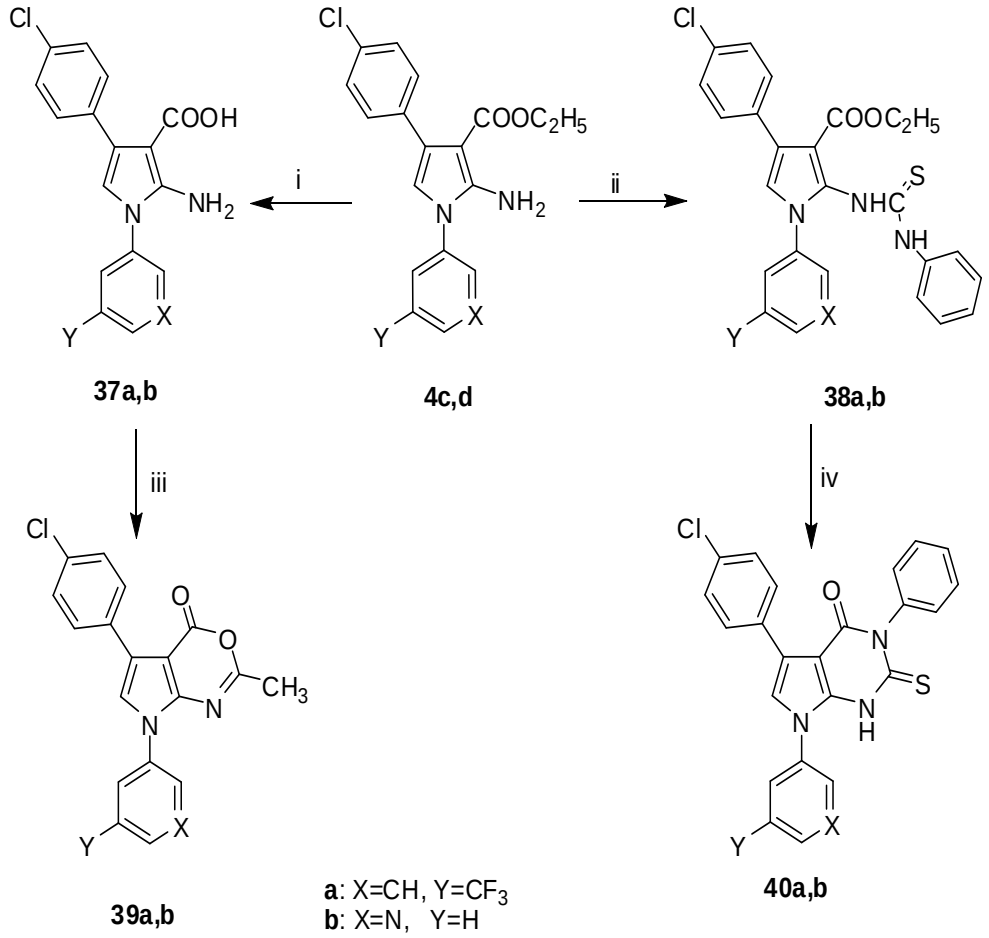
Scheme 8. Synthetic pathways for compounds **29a,b**, **30a,b**, **31a,b** and **32a,b**.



a: X=CH, Y=CF_3
b: X=N, Y=H

Reagents: (i) $NH_2NH_2.H_2O$ / EtOH /reflux; (ii) Ac_2O / reflux; (iii) glucose/ EtOH/ reflux

Scheme 9. Synthetic pathways for compounds **33a,b**, **34a,b**, **35a,b** and **36a,b**.



Reagents: (i) NaOH /EtOH / HOAc/ reflux; (ii) C_6H_5NCS/EtOH/reflux; (iii) Ac_2O/ reflux; (iv) NaOEt / reflux

Scheme 10. Synthetic pathways for compounds **37a,b**, **38a,b**, **39a,b** and **40a,b**.

Finally, the title carboxylic acid derivatives **37a,b** was obtained via refluxing of the *o*-aminoester compounds **4c,d** with ethanolic sodium hydroxide (**Scheme 10**). Also, our aim was extended to develop novel ethyl 1-(substitutedaryl)-4-(4-chlorophenyl)-2-(3-phenylthioureido)-1H-pyrrol-3-carboxylates **38a,b** which were obtained via refluxing of 2-aminopyrrole derivatives **4c,d** with phenylisothiocyanate in absolute ethanol. Furthermore, fused 2-methyloxazine-4-one rings are reported to be prepared from the reaction of different *o*-aminocarboxylic acid derivatives with excess acetic anhydride. Thus, the target 2-methyloxazine-4-one derivatives **39a,b** were synthesized via refluxing of the *o*-aminocarboxylic acid compounds **37a,b** in excess acetic anhydride. Finally, the thiourea derivatives **38a,b** were heated with sodium ethoxide under reflux to furnish the target 2-thioxopyrimidin-4-one derivatives **40a,b**.

2.2. Biology

All the newly synthesized compounds **4a-40b** were preliminarily evaluated for their anti-inflammatory and analgesic activities (using rat paw edema method and writhing test; respectively) as well as their gastric ulcerative effect (ulcerogenicity) an *in-vitro* antibacterial activity against *Staphylococcus aureus* (ATCC 25923) as a representative of Gram-positive bacteria; *Pseudomonas aeruginosa* (ATCC 27853) and *Escherichia coli* (ATCC 8739) as representatives of Gram-negative bacteria. The compounds were also evaluated for their *in-vitro* antifungal activity against *Candida albicans* (ATCC 10231) (using the cup diffusion technique).

2.2.1. Anti-Inflammatory and Analgesic Screening

For the tested compounds **4a-40b**, the percent of edema inhibition after 1-6 h and the percent inhibition of the writhing movements are presented in **Tables 1-6**.

Table 1. Anti-inflammatory and analgesic results for compounds of **Scheme 1** and **Scheme 2**.

	Mean ± S.D. (Percent edema inhibition)						**Analgesic activity**			
Comp. No.	1 h	2 h	3 h	4 h	5 h	6 h	Potency	No. of writhing movements	Percent inhibition	Potency
Control	0.23 ± 0.03 (----)	0.26 ± 0.05 (-----)	0.45 ± 0.01 (-----)	0.54 ± 0.08 (-----)	0.63 ± 0.04 (-----)	0.78 ± 0.12 (-----)	----	55	---	---
Indocin	0.22 ± 0.03 (11.73)	0.14 ± 0.03 (20.50)	0.21 ± 0.02 (44.12)	0.23 ± 0.04 (52.71)	0.22 ± 0.08 (69.5)	0.05 ± 0.02 (88.70)	1	9	83.63	**1**
4a	0.21 ± 0.03 (0.71)	0.25 ± 0.04 (4.23)	0.37 ± 0.03 (32.84)	0.5 ± 0.002 (21.06)	0.35 ± 0.06 (37)	0.32 ± 0.03 (50)	0.56	23	58.18	0.69
4b	0.34 ± 0.02 (6.31)	0.35 ± 0.03 (22.12)	0.36 ± 0.07 (37.20)	0.24 ± 0.02[a,b] (55.50)	0.16 ± 0.08[a,b] (73.5)	0.13 ± 0.03[a] (61.21)	0.69	15	72.72	0.86
4c	0.22 ± 0.03 (5.60)	0.26 ± 0.02 (13.21)	0.18 ± 0.02 (38.21)	0.33 ± 0.03 (43.10)	0.17 ± 0.04[a] (70.4)	0.13 ± 0.004[a] (74.16)	0.83	10	81.81	0.97
4d	0.21 ± 0.02 (8.81)	0.10 ± 0.02 (43.16)	0.22 ± 0.09 (56.32)	0.14 ± 0.01[a] (66)	0.22 ± 0.02 (72.4)	0.07 ± 0.03[a] **(90.97)**	**1.02**	6	89.09	**1.06**
5a	0.22 ± 0.02 (5.65)	0.21 ± 0.04 (23.08)	0.35 ± 0.04 (36.21)	0.25 ± 0.01[a,b] (54)	0.36 ± 0.05 (69.84)	0.13 ± 0.04[a,b] (79.42)	0.89	27	50.90	0.60
5b	0.23 ± 0.05 (8.70)	0.19 ± 0.04 (15.94)	0.38 ± 0.02 (29.50)	0.26 ± 0.05[a,b] (52.20)	0.24 ± 0.04[a,b] (61.90)	0.19 ± 0.01 **(89.07)**	**1.010**	18	67.27	0.80
5c	0.19 ± 0.06 (17.39)	0.44 ± 0.01 (36.50)	0.36 ± 0.01 (42.85)	0.37 ± 0.05 (55.36)	0.29 ± 0.02[a,b] (63.50)	0.22 ± 0.08[a] **(89.54)**	**1.011**	7	87.27	**1.04**
5d	0.21 ± 0.02 (6.19)	0.20 ± 0.02 (32.41)	0.26 ± 0.02 (23.47)	0.20 ± 0.03 (52.38)	0.40 ± 0.04 (59.61)	0.13 ± 0.004 **(89.67)**	**1.012**	8	85.45	**1.02**
6a	0.23 ± 0.02 (13.04)	0.21 ± 0.04 (19.23)	0.41 ± 0.01 (39.20)	0.37 ± 0.05 (43.56)	0.20 ± 0.07 (67.32)	0.36 ± 0.05 **(91.08)**	**1.02**	14	74.54	0.89
6b	0.37 ± 0.03 (11.15)	0.48 ± 0.08 (25.47)	0.32 ± 0.04 (48.89)	0.21 ± 0.02 (61.05)	0.21 ± 0.06 (71.08)	0.41 ± 0.01 **(91.96)**	**1.03**	8	85.45	**1.02**
7a	0.21 ± 0.02 (13.41)	0.44 ± 0.02 (17.31)	0.19 ± 0.04 (37.21)	0.22 ± 0.02 (51.31)	0.23 ± 0.02 (59.10)	0.36 ± 0.01 (61.24)	0.69	19	65.45	0.78
7b	0.22 ± 0.06 (11.35)	0.23 ± 0.07 (21.82)	0.41 ± 0.03 (19.07)	0.38 ± 0.02 (49.14)	0.19 ± 0.06 (61.24)	0.33 ± 0.02 (88.13)	0.99	11	80	0.95
8a	0.21 ± 0.03 (6.19)	0.20 ± 0.03 (27.81)	0.18 ± 0.06 (38.21)	0.21 ± 0.03 (40.11)	0.2 ± 0.08 (47.12)	0.34 ± 0.06 (56.02)	0.63	37	32.72	0.39
8b	0.14 ± 0.06 (7.41)	0.12 ± 0.06 (18.47)	0.32 ± 0.03[a] (22.46)	0.19 ± 0.04 (37.28)	0.33 ± 0.03 (43.62)	0.12 ± 0.06 (61.35)	0.69	33	40	0.47

Table 2. Anti-inflammatory and analgesic results for compounds of **Scheme 3**.

	Mean ± S.D. (Percent edema inhibition)							Analgesic activity		
Comp. No.	1 h	2 h	3 h	4 h	5 h	6 h	Potency	No. of writhing movements	Percent inhibition	Potency
9a	0.21 ± 0.03 (9.50)	0.25 ± 0.04 (5.17)	0.18 ± 0.02[a] (13.03)	0.43 ± 0.02 (28.67)	0.28 ± 0.08 (43.39)	0.21 ± 0.02[a] (60.66)	0.68	37	32.72	0.39
9b	0.22 ± 0.02 (2.17)	0.14 ± 0.05 (3.07)	0.48 ± 0.07 (11.4)	0.45 ± 0.09 (27.85)	0.12 ± 0.04 (31.59)	0.54 ± 0.08 (69.52)	0.78	27	50.90	0.60
9c	0.15 ± 0.06 (10.3)	0.44 ± 0.01 (16.5)	0.18 ± 0.04 (36.5)	0.34 ± 0.02 (43.41)	0.17 ± 0.03[a,b] (73.52)	0.46 ± 0.09 (89.10)	1	25	54.54	0.65
9d	0.19 ± 0.04 (15.9)	0.31 ± 0.02 (19.7)	0.42 ± 0.09 (32.8)	0.36 ± 0.02 (52.36)	0.25 ± 0.01[a,b] (78.65)	0.21 ± 0.04 **(89.72)**	**1.01**	23	58.18	0.69
10a	0.27 ± 0.02 (6.08)	0.43 ± 0.06 (22.5)	0.45 ± 0.05 (31.52)	0.23 ± 0.08 (41.37)	0.36 ± 0.05 (41.49)	0.22 ± 0.02 (59.43)	0.67	14	74.54	0.89
10b	0.19 ± 0.06 (17.3)	0.14 ± 0.03 (20.9)	0.37 ± 0.01 (31.73)	0.41 ± 0.07 (39.24)	0.23 ± 0.06 (43.26)	0.23 ± 0.08 (61.42)	0.69	12	78.81	0.94
10c	0.44 ± 0.08 (0.00)	0.23 ± 0.05 (16.4)	0.36 ± 0.05 (41.28)	0.21 ± 0.02 (48.31)	0.34 ± 0.02 (66.82)	0.22 ± 0.04 (80.42)	0.90	9	83.63	**1**
10d	0.41 ± 0.03 (4.18)	0.32 ± 0.01 (27.2)	0.12 ± 0.02 (39.31)	0.21 ± 0.06 (52.45)	0.45 ± 0.05 (71.34)	0.45 ± 0.05 **(89.83)**	**1.01**	7	87.27	**1.04**
11a	0.42 ± 0.01 (3.48)	0.24 ± 0.02 (8.31)	0.41 ± 0.01 (23.21)	0.33 ± 0.03 (45.32)	0.24 ± 0.02 (69.45)	0.21 ± 0.04 (88.40)	0.97	24	56.36	0.67
11b	0.16 ± 0.04 (7.32)	0.42 ± 0.04 (11.4)	0.48 ± 0.08 (22.91)	0.21 ± 0.05 (35.37)	0.22 ± 0.06 (63.49)	0.36 ± 0.05 (88.67)	0.99	23	58.18	0.69
12a	0.49 ± 0.003 (21.0)	0.32 ± 0.04 (33.6)	0.25 ± 0.06 (49.56)	0.34 ± 0.03 (61.52)	0.25 ± 0.11 (81.63)	0.12 ± 0.09[a] **(91.89)**	**1.03**	16	70.90	0.84
12b	0.19 ± 0.03 (17.4)	0.34 ± 0.03 (26.8)	0.44 ± 0.08 (58.32)	0.25 ± 0.04 (71.43)	0.09 ± 0.06 (83.51)	0.15 ± 0.12[a] **(92.04)**	**1.04**	13	76.36	0.91

Table 3. Anti-inflammatory and analgesic results for compounds of **Scheme 4**.

	Mean ± S.D. (Percent edema inhibition)							Analgesic activity		
Comp. No.	1 h	2 h	3 h	4 h	5 h	6 h	Potency	No. of writhing movements	Percent inhibition	Potency
13a	0.22 ± 0.06 (17.9)	0.23 ± 0.01 (0)	0.53 ± 0.08 (51.37)	0.21 ± 0.05 (41.32)	0.54 ± 0.04 (53.67)	0.37 ± 0.03 (61.40)	0.69	27	50.90	0.60
13b	0.19 ± 0.02 (12.4)	0.21 ± 0.05 (8.61)	0.47 ± 0.08 (39.55)	0.46 ± 0.05 (52.47)	0.18 ± 0.03 (62.43)	0.24 ± 0.02 (89)	1	25	54.54	0.65
14a	0.27 ± 0.02 (0)	0.18 ± 0.04 (0)	0.34 ± 0.01 (19.32)	0.36 ± 0.01 (27.74)	0.24 ± 0.06 (33.27)	0.21 ± 0.02 (42.85)	0.48	57	---	---
14b	0.36 ± 0.07 (3.69)	0.22 ± 0.03 (10.2)	0.35 ± 0.05 (17.86)	0.41 ± 0.07 (38.31)	0.21 ± 0.03 (41.84)	0.61 ± 0.04 (61.90)	0.69	43	21.81	0.26
15a	0.22 ± 0.07 (3.40)	0.17 ± 0.03 (7.39)	0.46 ± 0.03 (21.74)	0.34 ± 0.04 (11.15)	0.23 ± 0.02 (42.58)	0.22 ± 0.04 (55.80)	0.63	33	40	0.47
15b	0.22 ± 0.02 (7.39)	0.48 ± 0.08 (18.2)	0.35 ± 0.02 (34.58)	0.24 ± 0.02[a,b] (45.63)	0.35 ± 0.05 (51.43)	0.43 ± 0.01 (69.20)	0.78	29	47.27	0.56
16a	0.37 ± 0.03 (0)	0.31 ± 0.01 (13.4)	0.38 ± 0.02 (31.23)	0.24 ± 0.05 (43.51)	0.29 ± 0.02 (52.10)	0.36 ± 0.05 (66)	0.74	27	50.90	0.60
16b	0.46 ± 0.08 (11.5)	0.24 ± 0.03[a,b] (17.3)	0.35 ± 0.08 (41.30)	0.33 ± 0.04 (48.37)	0.24 ± 0.01[a,b] (61)	0.28 ± 0.03[a] (84)	0.94	23	58.18	0.69

[a,b]: Significantly different from control value and reference value at $P < 0.05$. •S.D. = Standard deviation.

Table 4. Anti-inflammatory and analgesic results for compounds of **Scheme 5** and **Scheme 6**.

	Mean ± S.D. (Percent edema inhibition)							Analgesic activity		
Comp. No.	1 h	2 h	3 h	4 h	5 h	6 h	Potency	No. of writhing movements	Percent inhibition	Potency
17a	0.05 ± 0.04 (76.40)	0.08 ± 0.01 (68.42)	0.18 ± 0.003 (66.41)	0.22 ± 0.02 (52)	0.14 ± 0.06 (49.42)	0.12 ± 0.06 (40.71)	0.46	10	81.81	0.97
17b	0.21 ± 0.05 (88.87)	0.21 ± 0.02 (71.31)	0.12 ± 0.04[a] (62.74)	0.13 ± 0.04 (58.04)	0.19 ± 0.04 (50.10)	0.18 ± 0.04 (55.37)	0.62	8	85.45	**1.02**
18a	0.21 ± 0.03 (45.32)	0.09 ± 0.003[a] (47.48)	0.25 ± 0.03 (51.21)	0.17 ± 0.05 (53.42)	0.48 ± 0.07 (57.39)	0.12 ± 0.06[a] (85)	0.96	19	65.45	0.78
18b	0.25 ± 0.04 (55)	0.32 ± 0.01 (56)	0.32 ± 0.01 (61.36)	0.10 ± 0.01 (50.21)	0.45 ± 0.09 (72.35)	0.43 ± 0.02 (87.21)	0.98	14	74.54	0.89
19a	0.27 ± 0.05 (17.40)	0.33 ± 0.04 (23.64)	0.45 ± 0.08 (59.41)	0.45 ± 0.05 (64)	0.45 ± 0.07 (70.26)	0.25 ± 0.04 **(90.63)**	**1.02**	12	78.81	0.94
19b	0.15 ± 0.06 (20.51)	0.23 ± 0.07 (31.36)	0.21 ± 0.02 (46.07)	0.39 ± 0.05 (57.42)	0.23 ± 0.07 (73)	0.24 ± 0.04[a,b] **(90.88)**	**1.02**	10	81.81	0.97
20a	0.24 ± 0.02 (4.21)	0.23 ± 0.03 (11.32)	0.25 ± 0.03 (30.22)	0.25 ± 0.04 (47)	0.26 ± 0.02 (59.41)	0.47 ± 0.07 (55.61)	0.63	27	50.90	0.60
20b	0.23 ± 0.04 (6.26)	0.23 ± 0.01 (14.21)	0.47 ± 0.06 (34.52)	0.22 ± 0.022 (44.39)	0.23 ± 0.03 (57.23)	0.47 ± 0.1 (63)	0.71	21	61.81	0.73
21a	0.23 ± 0.02 (11.65)	0.31 ± 0.04 (21.64)	0.33 ± 0.03 (33.61)	0.22 ± 0.03[a,b] (59)	0.36 ± 0.05 (68.32)	0.14 ± 0.03[a,b] (89)	1	25	54.54	0.65
21b	0.23 ± 0.05 (8.70)	0.29 ± 0.05 (26.87)	0.25 ± 0.05 (34.38)	0.25 ± 0.03[a,b] (62.43)	0.24 ± 0.05[a,b] (61.90)	0.18 ± 0.01 **(91.70)**	**1.03**	23	58.18	0.69
22a	0.17 ± 0.04 (0)	0.45 ± 0.02 (11.50)	0.24 ± 0.02 (22.84)	0.37 ± 0.05 (33.44)	0.19 ± 0.03[a,b] (42.31)	0.23 ± 0.08[a] (48.21)	0.54	55	---	---
22b	0.24 ± 0.02 (2.40)	0.25 ± 0.02 (8.43)	0.13 ± 0.02 (23.36)	0.21 ± 0.03 (38.36)	0.50 ± 0.04 (46.53)	0.12 ± 0.05 (49.57)	0.56	57	---	---
23a	0.23 ± 0.03 (12.04)	0.23 ± 0.06 (21.23)	0.37 ± 0.02 (44.20)	0.37 ± 0.05 (52.27)	0.23 ± 0.03 (72.21)	0.37 ± 0.03 **(89.93)**	**1.01**	12	78.81	0.94
23b	0.36 ± 0.04 (14.15)	0.43 ± 0.04 (27.31)	0.35 ± 0.03 (50)	0.21 ± 0.02 (63.25)	0.22 ± 0.06 (74.30)	0.42 ± 0.02 **(92.56)**	**1.04**	10	81.81	0.97

Table 5. Anti-inflammatory and analgesic results for compounds of **Scheme 7** & **Scheme 8**.

	Mean ± S.D. (Percent edema inhibition)							Analgesic activity		
Comp. No.	1 h	2 h	3 h	4 h	5 h	6 h	Potency	No. of writhing movements	Percent inhibition	Potency
24a	0.11 ± 0.04 (4.46)	0.23 ± 0.03 (27.35)	0.27 ± 0.06 (33.19)	0.31 ± 0.02 (44.12)	0.24 ± 0.07 (67.13)	0.42 ± 0.06 (79.47)	0.89	36	34.54	0.41
24b	0.25 ± 0.04 (16.32)	0.45 ± 0.05 (31.40)	0.58 ± 0.07 (22.38)	0.21 ± 0.05 (45.77)	0.21 ± 0.06 (65.09)	0.37 ± 0.05 (88.02)	0.99	29	47.27	0.56
25a	0.20 ± 0.01 (9.03)	0.42 ± 0.05 (12.57)	0.35 ± 0.05 (23.52)	0.22 ± 0.07 (0)	0.25 ± 0.04 (31.47)	0.21 ± 0.03 (51.38)	0.58	23	58.81	0.69
25b	0.18 ± 0.04 (13.40)	0.11 ± 0.02 (10.9)	0.36 ± 0.02 (19.83)	0.42 ± 0.10 (35.30)	0.22 ± 0.05 (43.06)	0.22 ± 0.07 (60.26)	0.68	20	63.63	0.76
26a	0.26 ± 0.03 (7.41)	0.14 ± 0.05 (13.45)	0.47 ± 0.06 (27.30)	0.46 ± 0.02 (47.44)	0.12 ± 0.02 (51.45)	0.53 ± 0.06 (66.42)	0.75	12	78.81	0.94
26b	0.36 ± 0.03 (11.15)	0.46 ± 0.02 (21.74)	0.31 ± 0.04 (38.61)	0.23 ± 0.02 (41.03)	0.22 ± 0.04 (53.02)	0.12 ± 0.04 (71.68)	0.81	10	81.81	0.97
27a	0.24 ± 0.02 (1.37)	0.46 ± 0.07 (5.49)	0.31 ± 0.02 (27.63)	0.22 ± 0.02 (32.10)	0.22 ± 0.05 (21.08)	0.43 ± 0.01 (37.35)	0.42	43	21.81	0.26
27b	0.15 ± 0.05 (7.31)	0.45 ± 0.01 (14.52)	0.34 ± 0.02 (31.82)	0.35 ± 0.04 (26.41)	0.28 ± 0.03[a,b] (33.50)	0.22 ± 0.02[a] (41.95)	0.47	36	34.54	0.41
28a	0.15 ± 0.03 (0)	0.46 ± 0.01 (15.30)	0.22 ± 0.02 (26.84)	0.36 ± 0.02 (32.45)	0.12 ± 0.05[a,b] (43.05)	0.22 ± 0.04[a] (59.31)	0.67	20	63.63	0.76
28b	0.23 ± 0.03 (0)	0.21 ± 0.08 (6.41)	0.15 ± 0.03 (29.30)	0.21 ± 0.02 (37.05)	0.40 ± 0.01 (51.56)	0.13 ± 0.07 (65.47)	0.74	18	67.27	0.80
29a	0.12 ± 0.02 (0)	0.24 ± 0.05 (2.51)	0.34 ± 0.02 (11.53)	0.39 ± 0.02 (26)	0.65 ± 0.03 (33.96)	0.35 ± 0.03 (41.32)	0.47	56	---	---
29b	0.35 ± 0.02 (3.21)	0.27 ± 0.02 (7.31)	0.25 ± 0.06 (0)	0.16 ± 0.02[a,b] (22.41)	0.14 ± 0.07[a,b] (40)	0.21 ± 0.04[a,b] (52.67)	0.59	54	---	---
30a	0.27 ± 0.01 (5.42)	0.07 ± 0.01[a] (10.42)	0.32 ± 0.03 (21.36)	0.14 ± 0.06 (33.12)	0.35 ± 0.08 (41.44)	0.14 ± 0.05[a] (44)	0.49	25	54.54	0.65
30b	0.24 ± 0.03 (0)	0.33 ± 0.03 (12.53)	0.45 ± 0.02 (23.64)	0.08 ± 0.02[a] (41.26)	0.32 ± 0.08 (32.36)	0.76 ± 0.03 (56.31)	0.63	20	63.63	0.76
31a	0.26 ± 0.03 (16.41)	0.32 ± 0.04 (22.64)	0.44 ± 0.07 (57.46)	0.45 ± 0.05 (62)	0.55 ± 0.07 (75.26)	0.23 ± 0.05 **(93.04)**	**1.04**	6	89.09	**1.06**
31b	0.14 ± 0.05 (20.89)	0.22 ± 0.07 (32.38)	0.31 ± 0.02 (47.09)	0.28 ± 0.04 (67.42)	0.23 ± 0.06 (77)	0.23 ± 0.05[a,b] **(93.86)**	**1.05**	4	92.72	**1.10**
32a	0.23 ± 0.03 (7.31)	0.24 ± 0.037 (16.42)	0.24 ± 0.03 (0)	0.24 ± 0.04 (43.39)	0.25 ± 0.07 (61.47)	0.46 ± 0.06 (80)	0.90	18	67.27	0.80
32b	0.27 ± 0.03 (6.27)	0.23 ± 0.02 (24.23)	0.37 ± 0.05 (37.42)	0.27 ± 0.03 (48.58)	0.22 ± 0.04 (73.63)	0.36 ± 0.09 (82.41)	0.93	15	72.72	0.86

Table 6. Anti-inflammatory and analgesic results for compounds of **Scheme 9** & **Scheme 10**.

	Mean ± S.D. (Percent edema inhibition)							Analgesic activity		
Comp. No.	1 h	2 h	3 h	4 h	5 h	6 h	Potency	No. of writhing movements	Percent inhibition	Potency
33a	0.03 ± 0.02 (3.24)	0.07 ± 0.04 (11)	0.17 ± 0.03[a] (23.51)	0.23 ± 0.02 (43)	0.16 ± 0.06 (44.61)	0.17 ± 0.06 (45.71)	0.51	22	60	0.71
33b	0.23 ± 0.06 (7.42)	0.22 ± 0.03 (15.41)	0.12 ± 0.04[a] (41)	0.12 ± 0.05 (0)	0.18 ± 0.03 (48.21)	0.19 ± 0.06 (59.42)	0.67	19	65.45	0.78
34a	0.34 ± 0.03 (7.31)	0.37 ± 0.01 (17.42)	0.17 ± 0.03 (33.76)	0.33 ± 0.06 (0)	0.16 ± 0.08 (68.41)	0.17 ± 0.05 (75.30)	0.85	15	72.72	0.86
34b	0.24 ± 0.05 (11.42)	0.14 ± 0.03 (0)	0.28 ± 0.05 (42.87)	0.15 ± 0.09 (59.42)	0.21 ± 0.03 (0)	0.03 ± 0.03 (77)	0.87	18	67.27	0.80
35a	0.36 ± 0.03 (10)	0.35 ± 0.03 (1.75)	0.46 ± 0.08 (18)	0.38 ± 0.05 (23.51)	0.44 ± 0.05 (25.61)	0.26 ± 0.07 (31.78)	0.36	60	---	---
35b	0.14 ± 0.05 (7.31)	0.34 ± 0.06 (4.67)	0.27 ± 0.03 (21.45)	0.34 ± 0.04 (0)	0.25 ± 0.08 (33.21)	0.26 ± 0.05[a,b] (36)	0.41	55	---	---
36a	0.24 ± 0.01 (0)	0.22 ± 0.02 (8.53)	0.23 ± 0.06 (22.31)	0.26 ± 0.04 (31.54)	0.23 ± 0.03 (39.52)	0.45 ± 0.06 (43.46)	0.49	37	32.72	0.39
36b	0.27 ± 0.04 (6.80)	0.24 ± 0.03 (13.45)	0.43 ± 0.08 (29.45)	0.25 ± 0.03 (35)	0.22 ± 0.06 (43.52)	0.46 ± 0.07 (59.42)	0.67	32	41.81	0.49
37a	0.21 ± 0.05 (0)	0.38 ± 0.04 (10.54)	0.17 ± 0.03 (21.56)	0.30 ± 0.02 (33.76)	0.29 ± 0.03 (44)	0.25 ± 0.03 (53.67)	0.60	44	20	0.23
37b	0.25 ± 0.04 (6.31)	0.25 ± 0.05 (18.65)	0.26 ± 0.08 (27)	0.16 ± 0.08 (31.43)	0.22 ± 0.09 (39.54)	0.24 ± 0.06 (55)	0.62	37	32.72	0.39
38a	0.23 ± 0.04 (7.65)	0.23 ± 0.06 (21.56)	0.54 ± 0.05 (37.78)	0.26 ± 0.02 (57.62)	0.12 ± 0.09 (73.24)	0.22 ± 0.09 (88)	0.99	17	69.09	0.82
38b	0.43 ± 0.02 (10.43)	0.25 ± 0.05 (25.64)	0.25 ± 0.03 (0)	0.28 ± 0.04 (50.42)	0.25 ± 0.09 (77.34)	0.49 ± 0.10[a,b] **(92.17)**	**1.04**	12	78.81	0.94
39a	0.22 ± 0.04 (0)	0.28 ± 0.03 (17.35)	0.23 ± 0.01 (23)	0.25 ± 0.03 (34.90)	0.28 ± 0.01 (0)	0.47 ± 0.07 (50)	0.56	39	29.09	0.34
39b	0.24 ± 0.02 (5.90)	0.21 ± 0.06 (11)	0.46 ± 0.08 (19.31)	0.21 ± 0.07 (39)	0.29 ± 0.05 (43.86)	0.47 ± 0.08 (58.31)	0.66	33	40	0.47
40a	0.28 ± 0.03 (0)	0.14 ± 0.04 (21.43)	0.43 ± 0.07 (37.30)	0.50 ± 0.05 (49)	0.17 ± 0.08 (72)	0.60 ± 0.04 **(90)**	**1.01**	18	67.27	0.80
40b	0.32 ± 0.04 (10.32)	0.44 ± 0.10 (37.32)	0.33 ± 0.03 (0)	0.27 ± 0.02 (41.03)	0.24 ± 0.04 (53.02)	0.12 ± 0.03 (86.68)	0.98	13	76.36	0.91

It was revealed from the results that, compounds **4d, 5b, 5c, 5d, 6a, 6b, 9c, 9d, 10d, 12a, 12b, 13b, 19a, 19b, 21b, 23a, 23b, 31a, 31b, 38b** and **40a** exerted highly potent anti-inflammatory effect, comparable to that of indomethacin (Indocin®) at 6 h interval post carrageenan showing inhibition potency ranging from 1.01% - 1.05%. While, compounds **4b, 4c, 5a, 7a, 7b, 8b, 9a, 9b, 9c, 10b, 10c, 11a, 11b, 13a, 13b, 14b, 15b, 16a, 16b, 18a, 18b, 20b, 21a, 24a, 25b, 26a, 26b, 28b, 32a, 32b, 34a, 34b, 38a** and **40b** exerted moderate anti-inflammatory activity at 6 h interval post carrageenan, comparable with that of indomethacin (Indocin®) showing inhibition potency ranging from 0.68% - 1%.

In addition to, compounds **4a, 8a, 10a, 14a, 15a, 22a, 22b, 25a, 27a, 27b, 28a, 29a, 29b, 30a, 30b, 33a, 33b, 35a, 35b, 36a, 36b, 37a, 37b, 39a** and **39b** which showed weak anti-inflammatory activity at 6 h interval less than indomethacin showing inhibition potency ranging from 0.36% - 0.67%. The activity profiles of all the previous compounds were the same as indomethacin (response increasing by time).

It is worth mentioning that, the highly potent compounds were those comprising 3-cyanopyrrole rings attached to different side chains in the 2 position, among these chains are the aryl imino function as in compounds **5b-d**, thiourea group as in compounds **9c,d** and ethoxymethyleneimino chain in compound **13b**. Also, compounds containing pyrrole-3-carboxylate with the 2 position either unsubstituted as in compound **4d** or substituted with thiourea side chain as compound **38b** were highly potent.

Furthermore, among the highly potent compounds were thefused pyrrolopyrimidine compounds bearing 2-thioxo function with different substituents in the 4 position. Among these groups in the 4 position was the amino group as compound **10d**, imino function in compounds **12a,b**, 4-thioxo function as in compounds **31a,b** and 4-oxo group as in compound **40a**. Also, the 4-chloropyrrolopyrimidine derivative **21b** as well as the 4-hydrazinopyrrolopyrimidine analogue 23b exhibited potent activity comparable to the reference drug Indomethacin (Indocin®).

Moreover, other fused pyrrole compounds such as the pyrrolopyridine-2-one derivatives **6a,b** and the pyrrolo[1,2,6]thiadiazine-2,4-dione analogues **19a,b** exerted excellent activity.

As revealed from the results presented in **Tables 1-3** that, compounds **4d, 5c, 5d, 6b, 10c, 10d, 17b, 31a** and **31b** exhibited the most potent analgesic activity with potency ranging from 1 - 1.10 to the reference drug Indomethacin. It is to be noted that some functions are assumed to be responsible for the highly potent analgesic activity of these compounds. Among these functions are the ester function in 3-position as in compound **4d**, the 2,4-dichlorobenzylidine imino function in pyrrole-2-position as in compounds **5c** and **5d** and pyrrolopyridine moiety in compound **6b**. Also, the pyrrolopyrimidine thione function as in compounds **10c** and **10d**.

Furthermore, the carboxamide function as in compound **17b** led to high analgesic activity. Additionally, pyrrolopyrimidine dithione function as in compounds **31a** and **31b** exerted the most potent analgesic activity.

2.2.2. Ulcerogenicity

Five compounds that exhibited the most potent anti-inflammatory activity; **12b, 23b, 31a, 31b** and **38b** were evaluated for their ulcerative effect on rats as revealed in **Table 7**.

Table 7. Ulcerogenic effects of the tested compounds.

Compounds	Control	Indomethacin	12b	23b	31a	31b	38b
% Ulceration	0.0	94	0.0	51.6	33.2	0.0	27.8

In general, all the tested compounds showed better results than the reference drug Indomethacin. Especially, compounds **12b** and **31b** which were devoid of any ulcerative effect compared to 94% of that of Indomethacin as illustrated in the previous table.

2.2.3. Anti-Microbial Screening

For the tested compounds **4a-40b**, the resulting inhibition zones were measured in mm diameter, **Tables 8-10**.

Among the tested compounds, compounds **5d, 9d, 11b, 12a, 13b, 15a, 15b, 17a, 22a, 27a, 32a, 33a, 39a** and **39b** were found to be the most active.

Table 8. Inhibition zones (IZ) in mm diameter for compounds of **Schemes 1-4**.

Comp. No.	*S. aureus*	*E. Coli*	*Ps. aeruginosa*	*C. albicans*
4a	9	10	12	12
4b	11	10	15	17
4c	11	10	13	11
4d	12	10	17	9
5a	10	10	15	16
5b	11	15	13	14
5c	11	20	18	16
5d	11	**25**	**26**	10
6a	10	20	15	16
6b	11	11	18	10
7a	11	11	10	15
7b	12	11	10	10
8a	10	20	20	11
8b	10	18	**22**	11
9a	10	12	14	20
9b	9	20	**20**	10
9c	9	18	**20**	9
9d	10	**25**	11	10
10a	10	20	14	13
10b	9	20	18	9
10c	11	14	**20**	10
10d	11	11	**20**	21
11a	12	9	**20**	9
11b	9	13	**30**	9
12a	10	**30**	14	20
12b	9	23	13	9
13a	10	24	16	18
13b	11	12	**30**	17
14a	9	14	11	9
14b	10	9	10	17
15a	9	**28**	17	9
15b	10	**40**	**20**	15
16a	10	13	17	14
16b	10	10	**20**	22
Ampicillin	30	22	27	-
Fluconazole	-	-	-	32

Table 9. Inhibition zones (IZ) in mm diameter for compounds of **Schemes 5-8**.

Comp. No.	*S. aureus*	*E. Coli*	*Ps. aeruginosa*	*C. albicans*
17a	15	18	**29**	20
17b	14	20	17	18
18a	10	23	13	**25**
18b	15	20	13	20
19a	13	20	18	**25**
19b	10	18	19	21
20a	10	13	11	16
20b	10	16	14	15
21a	9	13	19	9
21b	11	13	21	17
22a	11	12	**32**	14
22b	11	17	23	16
23a	10	12	18	12
23b	11	16	20	10
24a	13	20	14	10
24b	12	11	11	10
25a	12	15	19	10
25b	17	14	11	12
26a	9	23	19	9
26b	10	17	20	15
27a	10	24	**30**	15
27b	10	23	24	11
28a	9	10	12	14
28b	10	15	10	15
29a	10	13	12	13
29b	15	13	20	17
30a	19	12	12	15
30b	**26**	13	16	18
31a	10	13	13	10
31b	10	20	17	15
32a	9	12	**30**	17
32b	20	12	13	9
Ampicillin	30	22	27	-
Fluconazole	-	-	-	32

Table 10. Inhibition zones (IZ) in mm diameter for compounds of **Scheme 9** & **Scheme 10**.

Comp. No.	*S. aureus*	*E. Coli*	*Ps. aeruginosa*	*C. albicans*
33a	10	**30**	10	9
33b	9	13	14	8
34a	9	11	11	10
34b	9	10	15	9
35a	9	10	10	17
35b	9	10	10	13
36a	10	14	10	**23**
36b	10	12	24	14
37a	10	11	14	13
37b	9	11	12	10
38a	10	18	18	14
38b	10	20	12	9
39a	10	16	**40**	9
39b	10	19	**30**	10
40a	12	12	13	12
40b	12	10	10	9
Ampicillin	30	22	27	-
Fluconazole	-	-	-	32

Among the different functions attached to the free pyrrole ring which exerted potent antimicrobial activity against Gram negative bacteria are the 2,4-dichlorobenzylidineimino, thiourea, phenylurea, ethoxymethyleneimino as well as dimethylaminomethyleneimino groups as in compounds **5d**, **9d**, **11b**, **13b** and **15a**, **15b**; respectively, in addition to, the carboxamide and the acid hydrazide side chains attached to the pyrrole ring in compounds **17a** and **33a**; respectively.

Furthermore, functions surmounted on the pyrrolopyrimidine skeleton as 4-imino-3-phenyl-2-thione and 4-morpholino groups as in compounds **12a** and **22a**; respectively, also displayed significant antimicrobial activity. Besides to, the triazolopyrrolopyrimidine derivative **27a**, pyrrolotriazine analogue **32a** as well as the pyrroloxazine compounds **39a**, **39b** which exerted high antimicrobial activities against Gram negative bacteria. It is worth mentioning that, all compounds exerted weak activity against Gram positive bacteria except for the 3-imidazolidine substituted pyrrole derivative **30b** which exerted moderate antimicrobial activity. However, only the pyrrolopyrimidinone derivative **18a** and the 1,2,6-thiadiazine-2,4-dione analogue **19a** exerted moderate antifungal activity against C. albicans.

2.3. Computer Aided Docking

The most active twenty compounds as anti-inflammatory agents **4d**, **5b**, **5c**, **5d**, **6a**, **6b**, **9c**, **9d**, **10d**, **12a**, **12b**, **13b**, **19a**, **19b**, **21b**, **23b**, **31a**, **31b**, **38b and 40a** were subjected to docking using Molecular Operating Environment (MOE) program [36] on the 3D structure of the cyclooxygenase-2 enzyme (COX-2) in a trial to predict their mode of action as anti-inflammatory drugs.

2.3.1. Docking on the Active Site of Cyclooxygenase-2 Enzyme (COX-2)

1) *Diclofenac interactions with the active site of* COX-2:

Diclofenac interacted as hydrogen bond acceptor via four hydrogen bonds via both the oxygen atoms of car-

boxyl group with the amino acid residues Tyr 385 (2.73 A˚) and Ser 530 (2.65 A˚, 2.91 A˚ and 3.04 A˚) as shown in **Figure 1**.

2.3.2. Docking of Compound 4d into COX-2

Active site revealed that several molecular interactions were considered to be responsible for the observed affinity, as the N of pyridine moiety acted as a hydrogen bond acceptor with the side chain residue; His 90 (2.25 A˚) with a strength of 81.3%. In addition to a hydrogen bond interaction between the hydrogens of the amino group which acted as a hydrogen bond donor with the side chain residue Tyr 355 (2.61 A˚) with a strength of 5.3%. Besides to, hydrophobic interactions involving the pyridine C_6 and *p*-chlorophenyl C_3 carbon as well the CH_3 group of ester function and the following amino acid residues: His 90, Met 113, Val 116, Leu 117, Arg 120, Val 349, Leu 352, Ser 353, Tyr 355, Leu 359, Leu 384, Tyr 385, Trp 387, Phe 518, Met 522, Val 523, Gly 526, Ala 527, Ser 530 and Leu 531 as shown in **Figure 2**.

2.3.3. Docking of Compound 5b into COX-2

Active site revealed the presence of arene cation interaction between the pyrrole ring and the amino acid residue Arg 120. In addition to, hydrophobic interactions involving pyridine C_4 and C_6 carbons and the following amino acid residues: His 90, Met 113, Val 116, Leu 117, Arg 120, Val 349, Leu 352, Ser 353, Tyr 355, Leu 359, Trp 387, Arg 513, Phe 518, Met 522, Val 523, Ala 527, Ser 530 and Leu 531 as shown in **Figure 3**.

2.3.4. Docking of Compound 5c into COX-2

Active site illustrated the presence of several interactions of the cyano group with different amino acid residues as it acted as a hydrogen bond acceptor with the side chain residues; His 90, Tyr 355 and Arg 513 (3.35 A˚, 2.43 A˚ and 3.16 A˚; respectively) at a strength of 2.1%, 90.6% and 13.4%; respectively. This beside hydrophobic interactions among the cyano function and the following amino acid residues: His 90, Val 116, Leu 117, Arg 120, Gln 192, Val 349, Leu 352, Ser 353, Tyr 355, Leu 359, Tyr 385, Trp 387, Arg 513, Ala 516, Ile 517, Phe 518, Val 523, Gly 526, Ala 527, Ser 530 and Leu 531 as shown in **Figure 4**.

2.3.5. Docking of Compound 5d into COX-2

Active site revealed the presence of hydrogen bond interaction between the cyano group, as it acted as a hydrogen bond acceptor with the amino acid residue Ser 530 residue (3.32 A˚) with a strength of 1.8%. In addition to, arene cation interactions involving the *p*-chlorophenyl ring with the amino acid residue Phe 518 and the 2,4-dichlorophenyl ring with the amino acid residue Arg 120. There are also hydrophobic interactions involving the pyridine C_2, C_5, C_6 as well as the pyridine nitrogen atom with the following amino acid residues: His 90, Val 116, Arg 120, Val 349, Leu 352, Ser 353, Tyr 355, Leu 359, Leu 384, Phe 518, Met 522, Gly 526, Ala 527, Ser 530 and Leu 531 as shown in **Figure 5**.

2.3.6. Docking of Compound 6a into COX-2

Active site revealed the presence of four hydrogen bonds in which the cyano nitrogen acted as a hydrogen bond acceptor for three hydrogen bonds with the amino acid residues His 90, Arg 513 and Tyr 355 (2.82 A˚, 3.44 A˚ and 2.91 A˚; respectively) with a strength of 20.4%, 7% and 7.3%; respectively. While, the amino group acted as a hydrogen bond acceptor with the amino acid residue Tyr 355 residue (3.24 A˚) with a strength 5.5%. In addition to, hydrophobic interactions involving the carbonyl oxygen with the following amino acid residues: His 90, Met 113, Val 116, Leu 117, Arg 120, Ser 530, Val 349, Leu 352, Ser 353, Tyr 355, Leu 384, Try 385, Ala 527 and Leu 531 as shown in **Figure 6**.

2.3.7. Docking of Compound 6b into COX-2

Active site revealed the presence of four hydrogen bonds and two arenes cation interactions. In which the amino group acted as a hydrogen acceptor via three hydrogen bonds with the amino acid residues His 90, Tyr 355 and Arg 513 (2.25 A˚, 3.32 A˚ and 3.43 A˚; respectively) with a strength of 3.5%, 9.1% and 43.2%; respectively. While the cyano nitrogen atom acted as a hydrogen bond acceptor with the amino acid residue His 90 (3.41 A˚) with strength of 2.2%. In addition to, two arene cation interactions among the *p*-chlorophenyl moiety and the amino acid residue Arg 120 and Arg 513. Besides to hydrophobic interactions involving the pyridine ring, pyrrole C_2 carbons as well as the chlorine atom and the *p*-chlorophenyl C_3 carbon with the following amino acid re-

sidues: Pro 86, Val 89, His 90, Arg 120, Val 349, Leu 352, Tyr 355, Arg 513, Ala 516, Phe 518, Val 523, Glu 524, Gly 526, Ala 527 and Ser 530 as shown in **Figure 7**.

2.3.8. Docking of Compound 9c into COX-2

Active site revealed the presence of two hydrogen bond interactions between the cyano nitrogen, as it acted as a hydrogen bond acceptor with the amino acid residue side Arg 120 and Tyr 355 (3.21 A˚ and 1.60 A˚; respectively) with a strength of 12.3% and 95.9%; respectively. In addition to, hydrophobic interactions involving the cyano nitrogen and chlorine atom with many amino acid residues: His 90, Val 349, Leu 352, Ser 353, Tyr 355, Leu 359, Phe 381, Tyr 385, Trp 387, Arg 513, Ala 516, Val 523, Gly 526, Ala 527, Ser 530 and Leu 531 as shown in **Figure 8**.

2.3.9. Docking of Compound 9d into COX-2

Active site revealed the presence of one hydrogen bond between the pyridyl nitrogen atom as it acted as a hydrogen bond acceptor with the amino acid residue His 90 (2.82 A˚) with a strength of 4.8%. In addition to, hydrophobic interactions concerning 4-chlorophenyl C_2 carbon, pyridine C_2 and C_4 carbons, the thiourea amino group and sulphur atom with the following amino acid residues: His 90, Arg 120, Val 349, Leu 352, Ser 353, Tyr 355, Phe 381, Leu 384, Tyr 385, Trp 387, Met 522, Val 523, Gly 526 and Ala 527 as shown in **Figure 9**.

2.3.10. Docking of Compound 10d into COX-2

Active site revealed hydrogen bond interaction between the N atom of pyridine moiety as it acted as a hydrogen bond acceptor with the side chain residues His 90 and Arg 513 (2.74 A˚ and 3.54 A˚; respectively) with a strength of 21.7% and 1.2%; respectively. Besides to, arene cation interaction between the *p*-chlorophenyl ring and the amino acid residue Arg 120. In addition to, hydrophobic interactions among the *p*-chloro phenylC_2 carbon, chlorine atom as well as the pyrimidine thioxo function, N_3 atom and C_4 carbon with the following amino acid residues: His 90, Val 116, Arg 120, Val 349, Leu 352, Ser 353, Leu 359, Trp 387, Arg 513, Ala 516, Ile 517, Phe 518, Met 522, Val 523 and Ala 527 as shown in **Figure 10**.

2.3.11. Docking of Compound 12a into COX-2

Active site revealed the presence of only hydrophobic interactions involving the phenyl C_2 carbon and the *p*-chlorophenyl C_3 and C_6 carbons as well as the chlorine atom with the following amino acid residues: His 90, Met 113, Val 116, Arg 120, Ile 345, Val 349, Leu 352, Ser 353, Tyr 355, Leu 359, Tyr 385, Arg 513, Ala 516, Phe 518, Met 522, Val 523, Gly 526, Ala 527, Ser 530 and Leu 531 as shown in **Figure 11**.

2.3.12. Docking of Compound 12b into COX-2

Active site showed the presence of a hydrogen bond interaction between imine function, as it acted as a hydrogen bond acceptor with the side chain Tyr 355 residue (3.15 A˚) with a strength of 6.3%. In addition to hydrophobic interactions involving the chlorine atom and the pyridyl C_6 carbon with many amino acid residues: His 90, Val 116, Arg 120, Val 349, Leu 352, Ser 353, Leu 384, Tyr 385, Trp 387, Phe 518, Met 522, Val 523, Gly 526, Ala 527 and Leu 531 as shown in **Figure 12**.

2.3.13. Docking of Compound 13b into COX-2

Active site showed hydrophobic interactions concerning the chlorine atom, cyano nitrogen and the methylene imino side chain with many amino acid residues: His 90, Met 113, Val 116, Arg 120, Leu 331, Ile 345, Val 349, Leu 352, Ser 353, Tyr 355, Leu 359, Val 523, Ala 527, Ser 530 and Leu 534 as shown in **Figure 13**.

2.3.14. Docking of Compound 19a into COX-2

Active site revealed the presence of two hydrogen bond interactions between the oxygen atom of pyrimidine C_4 oxo function as it acted as a hydrogen bond acceptor with the side chain residues Arg 120 and Tyr 355 (2.63 A˚ and 3.04 A˚; respectively) with a strength of 19.6% and 12.5%; respectively. In addition to hydrophobic interactions involving the pyrimidine N_3 and 2-oxo functions as well as pyrrole C_5 and *p*-chlorophenyl C_2 and C_6 carbons with many amino acid residues: Pro 86, Val 89, His 90, Arg 120, Tyr 348, Val 349, Leu 352, Tyr 355, Tyr 385, Trp 387, Arg 513, Met 522, Val 523, Glu 524, Gly 526, Ala 527 and Leu 531 as shown in **Figure 14**.

2.3.15. Docking of Compound 19b into COX-2

Active site revealed the presence of hydrogen bond interactions between the oxygen atoms of pyrimidine C_2 and C_4 oxo functions as they acted as hydrogen bond acceptor with the side chain residue Arg 513 (3.27 A˚, 2.3%) and Arg 120 (2.28 A˚, 9.5%); respectively. In addition to, another hydrogen bond between the pyridyl nitrogen atom as it acted as hydrogen bond acceptor with the amino acid residue Arg 513 (3.45 A˚, 1.7%). In addition to, hydrophobic interactions concerning the carbon atoms of *p*-chlorophenyl moiety and the following amino acid residues: Pro 86, His 90, Arg 120, Gln 192, Val 349, Leu 352, Ser 353, Tyr 355, Arg 513, Ala 516, Val 523, Glu 524, Ala 527, Ser 530 and Leu 531 as shown in **Figure 15**.

2.3.16. Docking of Compound 21b into COX-2

Active site revealed the presence of hydrogen bond interaction between the N_1 of the pyrimidine moiety, as it acted as a hydrogen bond acceptor with the side chain residue Arg 120 (2.35 A˚) with strength of 64.2%. In addition to, arene cation interaction between the pyridine moiety and the amino acid residue Arg 120. Besides to, hydrophobic interactions involving the pyrimidine C_2 carbon, pyrrole C_5 carbon and pyridine C_6 carbon with many amino acid residues: Arg 120, Val 349, Leu 352, Tyr 355, Tyr 385, Trp 387, Arg 513, Val 523, Glu 524, Gly 526, Ala 527 and Leu 531 as shown in **Figure 16**.

2.3.17. Docking of Compound 23b into COX-2

Active site revealed the presence of three hydrogen bond interactions in which the hydrazine NH_2 proton acted as a hydrogen bond donor with the amino acid residue Val 349 (3.21 A˚, 1.5%), while the nitrogen atom acted as a hydrogen bond acceptor with the amino acid residue Ser 353 (2.62 A˚, 2.5%). Also, the hydrazine NH proton acted as a hydrogen bond donor to the amino acid residue Val 349 (1.38 A˚, 93.7%). Besides to, hydrophobic interactions among the *p*-chlorophenyl moiety and the pyrimidine C_4 carbon with the following amino acid residues: His 90, Tyr 348, Val 349, Leu 352, Ser 353, Tyr 355, Phe 381, Leu 384, Tyr 385, Phe 518, Met 522, Val 523, Gly 526, Ala 527 and Ser 530 as shown in **Figure 17**.

2.3.18. Docking of Compound 31a into COX-2

Active site showed arene cation interaction between the 3-triflouromethylphenyl ring and the amino acid residue Arg 513. In addition to, hydrophobic interactions involving the 3-trifluoromethylphenyl C_6 and fluorine atom as well as the two sulphur atoms of the two thioxo functions of pyrimidine ring with the following amino acid residues: His 90, Gln 192, Val 349, Leu 352, Ser 353, Tyr 355, Leu 384, Tyr 385, Trp 387, Arg 513, Ala 516, Ile 517, Phe 518, Met 522, Val 523, Gly 526, Ala 527 and Ser 530 as shown in **Figure 18**.

2.3.19. Docking of Compound 31b into COX-2

Active site revealed the presence of hydrophobic interactions involving the pyridine C_6 carbon, chlorine atom, the sulphur atom of the 2-thioxo function of pyrimidine ring as well as the pyrimidine N_3 NH moiety with the following amino acid residues: His 90, Val 349, Leu 352, Ser 353, Tyr 355, Leu 384, Tyr 385, Trp 387, Arg 513, Phe 518, Met 522, Val 523, Gly 526, Ala 527 and Leu 531 as shown in **Figure 19**.

2.3.20. Docking of Compound 38b into COX-2

Active site showed one hydrogen bond between NH-phenyl proton which acted as a hydrogen bond donor with the side chain residue Tyr 355 (2.03 A˚, 0.8%). In addition to, two arene cation interactions between both pyridine and phenyl rings and the amino acid residue Arg 120. Besides to, hydrophobic interactions involving the phenyl C_4 carbon and the sulphur atom with many amino acid residues: Pro 86, Val 116, Arg 120, Tyr 348, Val 349, Leu 352, Ser 353, Tyr 355, Leu 359, Tyr 385, Trp 387, Arg 513, Val 523, Glu 524, Gly 526, Ala 527, Ser 530 and Leu 531 as shown in **Figure 20**.

2.3.21. Docking of Compound 40b into COX-2

Active site revealed the presence of hydrophobic interactions involving the *p*-chlorophenyl C_2 carbon and pyrrole C_2 carbon with many amino acid residues: His 90, Met 113, Val 116, Leu 117, Arg 120, Ile 345, Val 349, Leu 352, Ser 353, Tyr 355, Leu 359, Tyr 385, Trp 387, Arg 513, Ala 516, Val 523, Gly 526, Ala 527, Ser 530 and Leu 531 as shown in **Figure 21**.

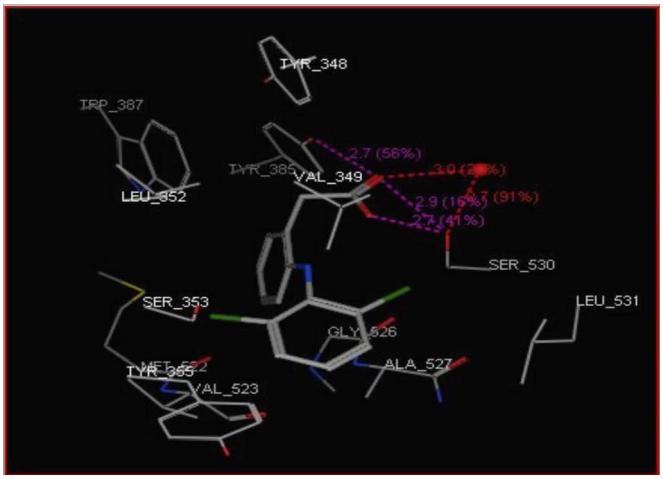


Figure 1. Docking of Diclofenac into the active site of COX-2.

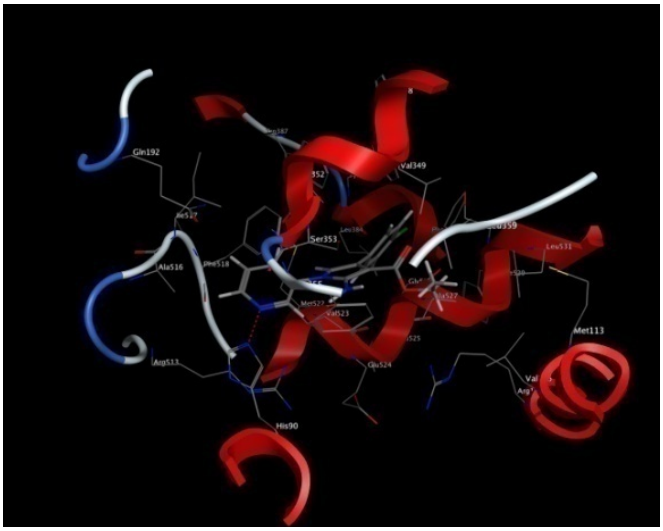


Figure 2. Docking of compound 4d into the active site of COX-2.

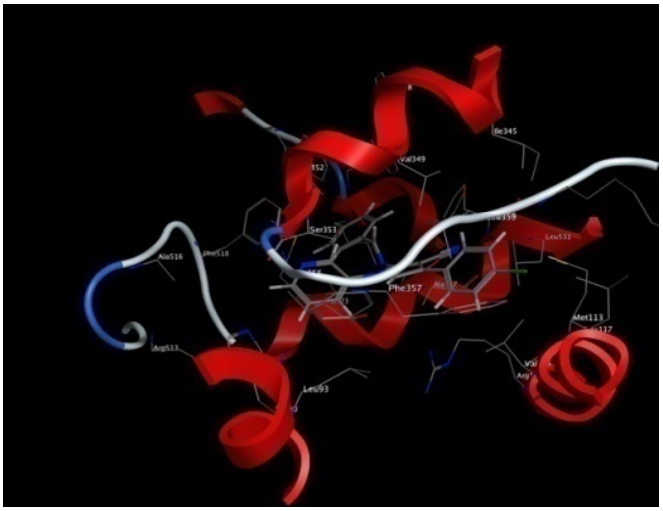


Figure 3. Docking of compound 5b in the active site of COX-2.

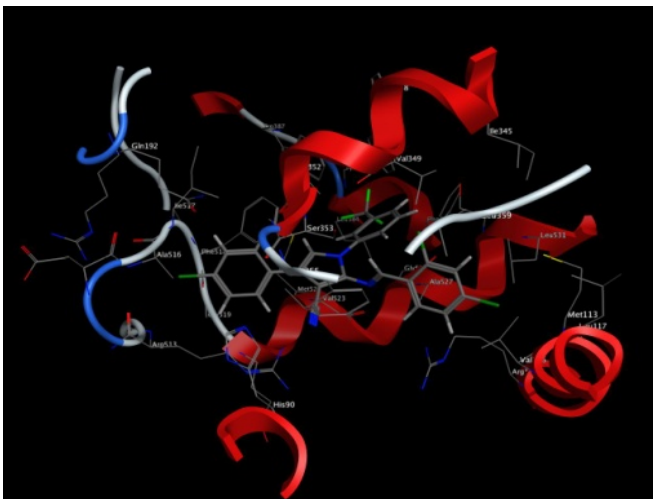


Figure 4. Docking of compound 5c in the active site of COX-2.

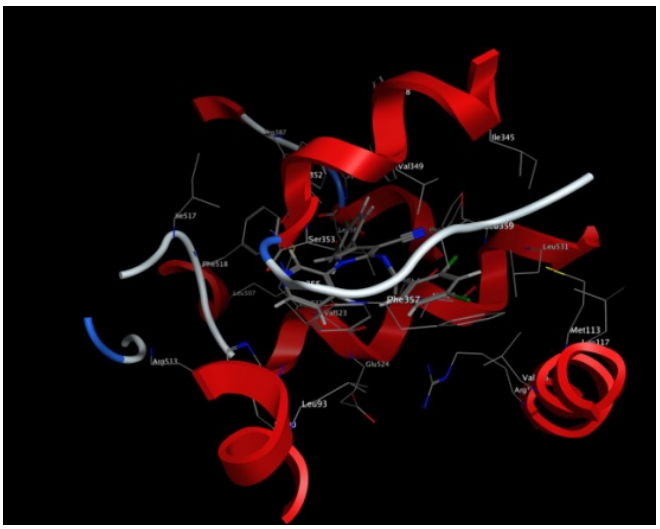


Figure 5. Docking of compound 5d in the active site of COX-2.

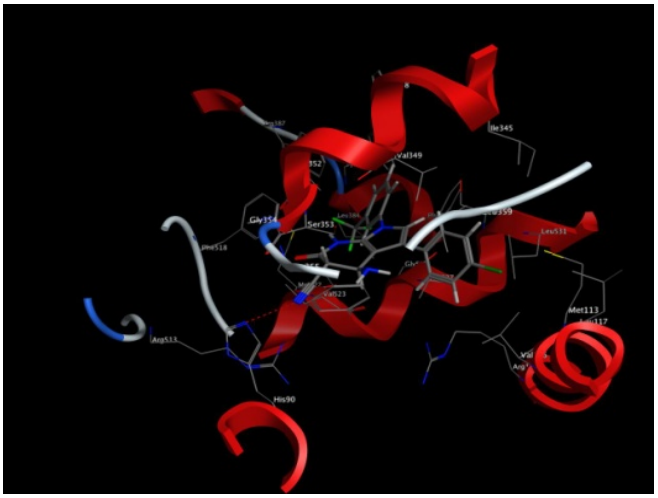


Figure 6. Docking of compound 6a in the active site of COX-2.

Figure 7. Docking of compound 6b in the active site of COX-2.

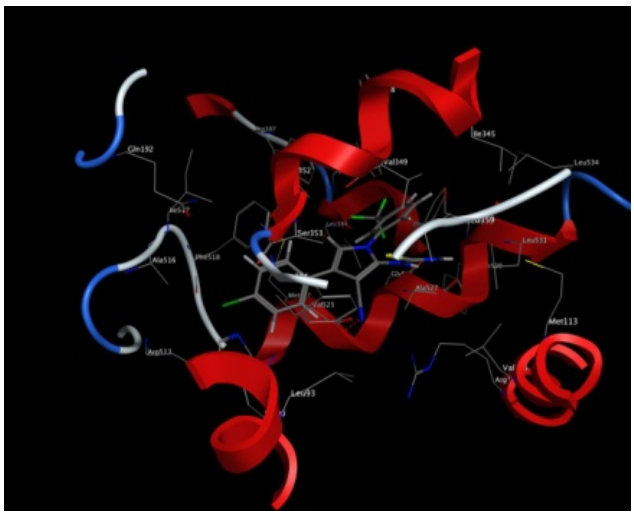


Figure 8. Docking of compound 9c in the active site of COX-2.

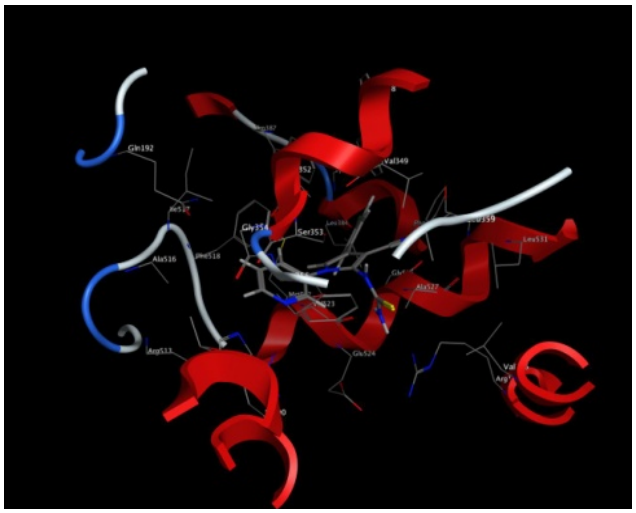


Figure 9. Docking of compound 9d in the active site of COX-2.

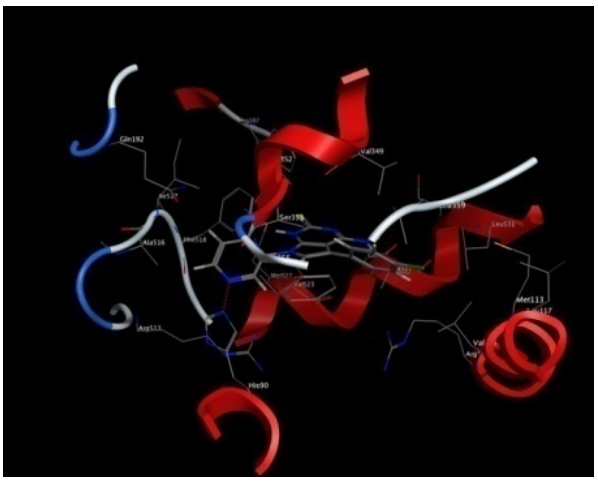


Figure 10. Docking of compound 10d in the active site of COX-2.

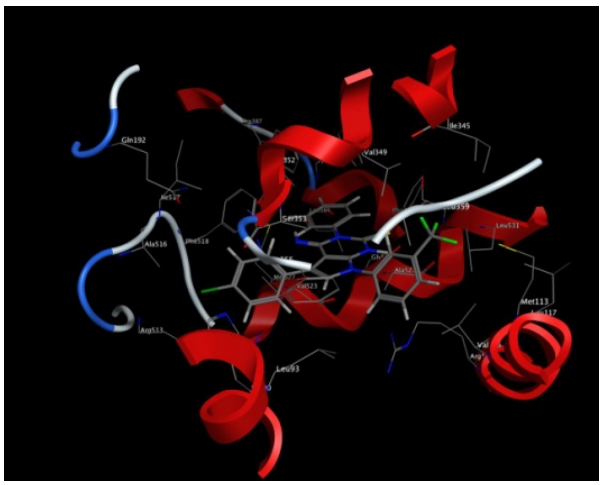


Figure 11. Docking of compound 12a in the active site of COX-2.

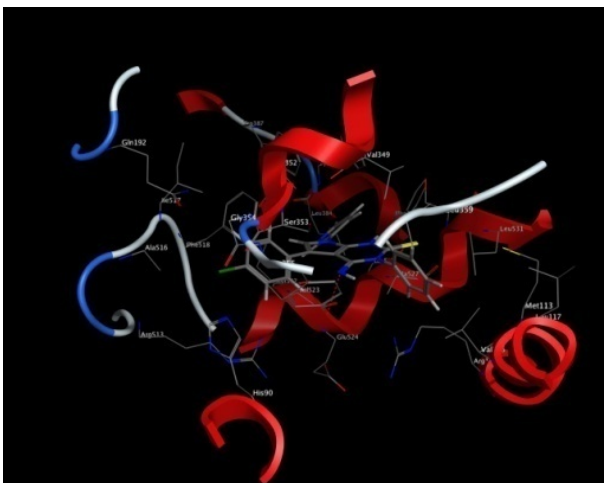


Figure 12. Docking of compound 12b in the active site of COX-2.

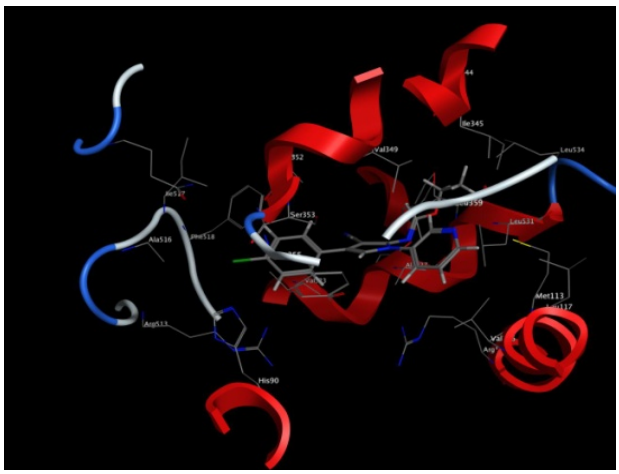


Figure 13. Docking of compound 13b in the active site of COX-2.

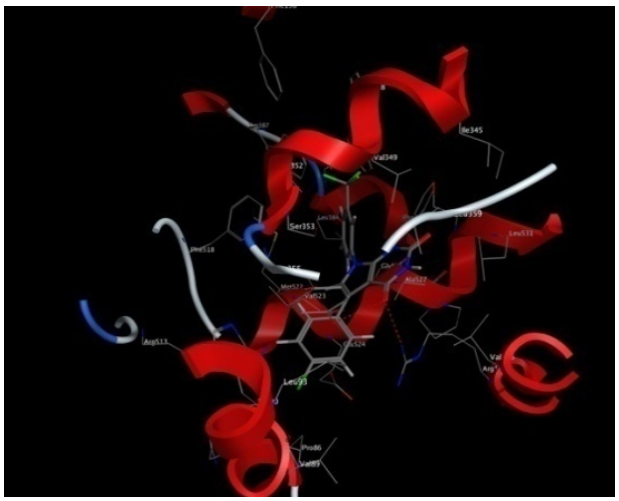


Figure 14. Docking of compound 19a in the active site of COX-2.

Figure 15. Docking of compound 19b in the active site of COX-2.

Figure 16. Docking of compound 21b in the active site of COX-2.

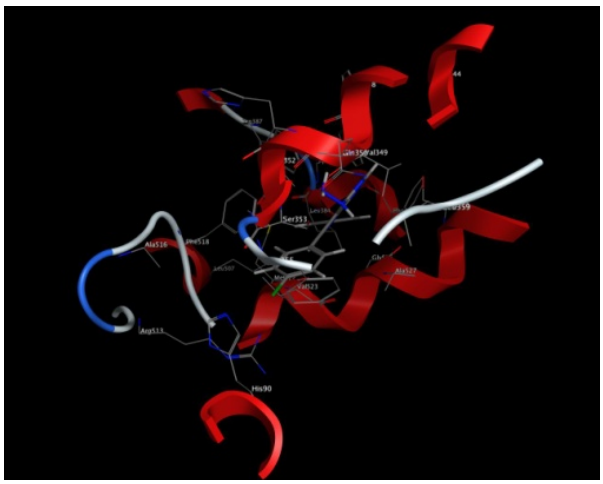


Figure 17. Docking of compound 23b in the active site of COX-2.

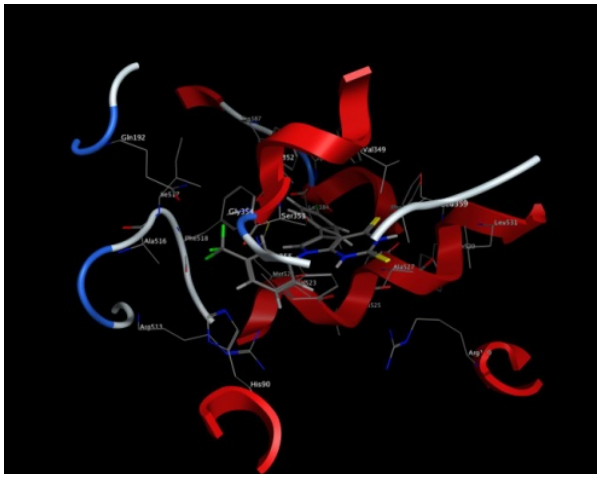


Figure 18. Docking of compound 31a in the active site of COX-2.

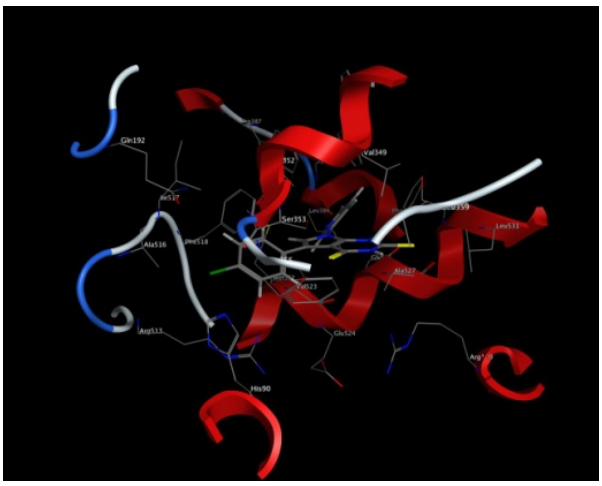


Figure 19. Docking of compound 31b in the active site of COX-2.

Figure 20. Docking of compound 38b in the active site of COX-2.

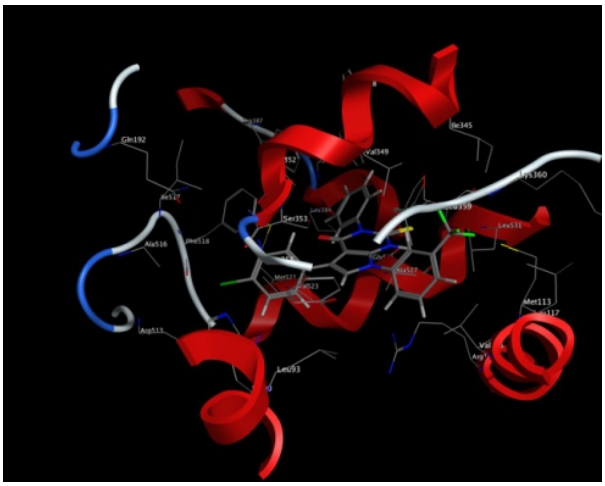


Figure 21. Docking of compound 40b in the active site of COX-2 enzyme.

3. Experimental

3.1. Chemistry

All melting points were measured on Electro thermal LA 9000 SERIS, Digital Melting point Apparatus and are uncorrected. IR spectra (KBr) were recorded on FT-IR 200 spectrophotometer (ύ·cm^{-1}), pharmaceutical analytical unit, Faculty of Pharmacy, Al-Azhar University. ^{1}H-NMR spectra were recorded in (DMSO-d_6) at 300 MHz on a Varian Gemini NMR spectrometer (δ ppm) using TMS as an internal standard, ResearchService Unit, Faculty of Science, Cairo University. Mass spectra were recorded on GC MS-QP 5050A mass spectrometer at 70 eV andmicroanalytical data were performed on Elementar Vario EI III CHN analyzer at the microanalytical unit, in Regional center for Mycology and Biotechnology, Al-Azhar University. Thin layer chromatography was performed on precoated (0.25 mm) silica gel GF254 plates (E. Merck, Germany). Compounds were detected with UV lamp at λ 254 nm.

3.1.1. 1-(4-Chlorophenyl)-2-(3-Trifluoromethylphenylamino)Ethanone; 3a

Equimolar amounts of 4-chlorophenacyl bromide (0.38 g, 2 mmol.) and 3-triflormethylaniline (0.32 g, 0.25 mL, 2 mmol.) were refluxed for 4 h in absolute ethanol (25 mL) in presence of drops of TEA, then left to cool. The solid product was collected by filtration after cooling and recrystallized from ethanol.

Fluffy golden yellow needle crystals; yield (90%); m.p.:138˚C. **IR [KBr, cm^{-1}]**: 3370 (NH); 3079 (CH aromatic); 2912 (CH aliphatic); 1691 (C=O); 1522 (C=C); 1108 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d_6, δ ppm)**: 4.76 (s, 2 H, CH_2CO); 6.39 (s, 1 H, NH, D_2O exchangeable); 6.82 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 6.94 (d, 1 H, *J* = 7.2 Hz, 3-CF_3-C_6H_4-C_6-H); 6.97-7.00 (m, 1 H, 3-CF_3-C_6H_4-C_4-H); 7.25-7.30 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.64 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 8.11 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H). **Anal. Calc.** (%) for $C_{15}H_{11}ClF_3NO$ (313.7): C, 57.43; H, 3.53; N, 4.46. **Found** (%): C, 57.52; H, 3.55; N, 4.48.

3.1.2. 1-(4-Chlorophenyl)-2-(Pyridin-3-Ylamino)Ethanone; 3b

An equimolar mixture of 4-chlorophenacyl bromide (0.38 g, 2 mmol.) and 3-aminopyridine (0.19 g, 2 mmol.) were stirred for 2 h. at room temperature in (20 mL) diethyl ether. The solid product was collected by filtration and recrystallized from the ethanol.

Buff needle crystals; yield (95%); m.p.: 205 ˚C. **IR [KBr, cm^{-1}]**: 3332, 3220 (NH); 3060 (CH aromatic); 2929 (CH aliphatic); 1693 (C=O); 1636 (C=N); 1585 (C=C); 1084 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 248 ($M^{+\bullet}$+2, 3); 246 ($M^{+\bullet}$, 11); 139 (100). **Anal**. **Calc**. (%) **for** $C_{13}H_{11}ClN_2O$ (246.7): C, 63.29; H, 4.49; N, 11.36. **Found** (%): C, 63.32; H, 4.57; N, 11.33.

3.1.3. General Procedure for Synthesis of Compounds 4a-d

The selected 2-(substitutedamino)-1-(4-chlorophenyl)ethanones **3a,b** (0.01 mol.) was stirred at room temperature with the appropriate nitrile (0.01 mol.) namely; malononitrile and ethylcyanoacetate in (40 mL) sodium ethoxide [prepared by dissolving sodium metal (0.23 g, 0.01 mol.) in absolute ethanol (40 mL)] overnight. The obtained product was filtered, washed with water then recrystallized from glacial acetic acid.

1) 2-Amino-4-(4-chlorophenyl)-1-(3-trifluoromethylphenyl)-1H-pyrrole-3-carbonitrile; 4a.

Yellow needle crystals; yield (63%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3427, 3300 (NH_2); 2900 (CH aliphatic); 2224 (C≡N); 1561 (C=C); 1023 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d_6, δ ppm)**: 7.07 (s, 1 H, CH-pyrrole); 7.22 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.31-7.38 (m, 3 H, 3-CF_3-C_6H_4-$C_{4,5,6}$-H); 7.64 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 7.86 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.45 (s, 2 H, NH_2, D_2O exchangeable). **^{13}C NMR (DMSO-d_6, δ ppm)**: 108 (pyrrole-C_3); 112 (3-CF_3-C_6H_4-C_2); 115 (C≡N); 118 (pyrrole-C_5); 120 (pyrrole-C_2); 122 (3-CF_3-C_6H_4-C_4); 125.7 (CF_3); 127.5 (3-CF_3-C_6H_4-C_6); 127.6 (pyrrole-C_4); 127.9 (4-Cl-C_6H_4-$C_{2,6}$); 128.1 (4-Cl-C_6H_4-$C_{3,5}$); 128.5 (3-CF_3-C_6H_4-C_5); 131.4 (3-CF_3-C_6H_4-C_3); 132.2 (4-Cl-C_6H_4-C_4); 132.5 (4-Cl-C_6H_4-C_1); 142 (3-CF_3-C_6H_4-C_1); **MS** m/z (relative intensity %): 363 ($M^{+\bullet}$+2) (0.3); 361 ($M^{+\bullet}$) (0.2); 76 (100). **Anal**. **Calc**. (%) **for** $C_{18}H_{11}ClF_3N_3$ (361.7): C, 59.76; H, 3.06; N, 11.62. **Found** (%): C, 59.80; H, 3.14; N, 11.68.

2) 2-Amino-4-(4-chlorophenyl)-1-(pyridin-3-yl)-1H-pyrrole-3-carbonitrile; 4b**.**

Dark grey crystals; yield (77%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3445, 3200 (NH_2); 3080 (CH aromatic); 2880 (CH aliphatic); 2191 (C≡N); 1638 (C=N); 1598 (C=C); 1091 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 294 ($M^{+\bullet}$, 3); 112 (100). **Anal**. **Calc**. (%) **for** $C_{16}H_{11}ClN_4$ (294.7): C, 65.20; H, 3.76; N, 19.01. **Found** (%): C,

65.83; H, 4.01; N, 19.54.

3) Ethyl 2-amino-4-(4-chlorophenyl)-1-(3-trifluoromethylphenyl)-1H-pyrrole-3-carboxylate; 4c

Orange needle crystals; yield (57%); m.p.: 250˚C - 252˚C C. **IR [KBr, cm^{-1}]**: 3442, 3200 (NH_2); 3060 (CH aromatic); 2960 (CH aliphatic); 1728 (C=O); 1280, 1060 (C-O-C); 1121 (*p*-Cl-phenyl). **MS** m/z (relative intensity %): 410 ($M^{+\bullet}$+2, 2); 409 ($M^{+\bullet}$+1, 0.4); 161 (100). **Anal**. **Calc**. (%) **for** $C_{20}H_{16}ClF_3N_2O_2$ (408.8): C, 58.76; H, 3.94; N, 6.85. **Found** (%): C, 58.80; H, 4.01; N, 6.82.

4) Ethyl 2-amino-4-(4-chlorophenyl)-1-(pyridin-3-yl)-1H-pyrrole-3-carboxylate; 4d

Brown crystals**;** yield (69%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3360, 3250 (NH_2); 3002 (CH aromatic); 2819 (CH aliphatic); 1720 (C=O); 1641 (C=N); 1530 (C=C); 1259, 1089 (C-O-C); 1147 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 1.25 - 1.30 (m, 3 H, CH_2CH_3); 3.50 - 3.59 (m, 2 H, CH_2CH_3); 6.72 (s, 2 H, NH_2, D_2O exchangeable); 7.30 (d, 2 H, *J* = 8.3 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.55 - 7.58 (m, 1 H, pyridyl-C_5-H); 7.64 - 7.72 (m, 1 H, pyridyl-C_6-H); 7.85 (d, 2 H, *J* = 8.3 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.92 (s, 1 H, CH-pyrrole); 8.03 - 8.06 (m, 1 H, pyridyl-C_4-H); 8.51 (s, 1 H, pyridyl-C_2-H). **Anal**. **Calc**. (%) **for** $C_{18}H_{16}ClN_3O_2$ (341.8): C, 63.25; H, 4.72; N, 12.29. **Found** (%): C, 63.75; H, 4.98; N, 12.78.

3.1.4. General Procedure for Synthesis of Compounds 5a-d

An equimolar mixture of the appropriate 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and the selected aromatic aldehyde namely; benzaldehyde and 2,4-dichlorobenzaldehyde (2 mmol.) was heated under reflux for 16 h in absolute ethanol (30 mL) containing glacial acetic acid (2 - 3 drops). The reaction mixture was allowed to cool and the product was filtered off, washed with ethanol and recrystallized from dioxane.

1) 2-(Benzylidenimino)-4-(4-chlorophenyl)-1-(3-trifluoromethylphenyl)-1H-pyrrole-3-carbonitrile; 5a

Faint yellow needle crystals; yield (55%); m.p.: 280˚C - 282˚C. **IR [KBr, cm^{-1}]**: 2927 (CH aromatic); 2863 (CH aliphatic); 2223 (C≡N); 1634 (C=N); 1560 (C=C); 1023 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 6.77 - 6.88 (m, 3 H, C_6H_5-$C_{3,4,5}$-H); 7.03 (d, 2 H, *J* = 8.1Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.25 (s, 1 H, CH-pyrrole); 7.30 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.34 - 7.37 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.45 - 7.50 (m, 2 H, 3-CF_3-C_6H_4-$C_{4,6}$-H); 7.85 (d, 2 H, *J* = 8.1 Hz,C_6H_5, $C_{2,6}$-H); 8.36 (s, 1 H, CH-benzylidinimine); 8.49 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); **MS** m/z (relative intensity %): 450 ($M^{+\bullet}$+1) (0.4); 449 ($M^{+\bullet}$, 0.5); 448 ($M^{+\bullet}$-1, 0.5); 83 (100). **Anal**. **Calc**. (%) **for** $C_{25}H_{15}ClF_3N_3$ (449.9): C, 66.75; H, 3.36; N, 9.34. **Found** (%): C, 66.82; H, 3.58; N, 9.74.

2) 2-(Benzylidenimino)-4-(4-chlorophenyl)-1-(pyridin-3-yl)-1H-pyrrole-3-carbonitrile; 5b

Dark brown powder; yield (67%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 2926 (CH aromatic); 2864 (CH aliphatic); 2207 (C≡N); 1585 (C=N); 1562 (C=C); 1105 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 384 ($M^{+\bullet}$+2, 0.5); 383 ($M^{+\bullet}$+1, 0.1); 382 ($M^{+\bullet}$, 0.1); 67 (100). **Anal**. **Calc**. (%) **for** $C_{23}H_{15}ClN_4$ (382.8): C, 72.16; H, 3.95; N, 14.63. **Found** (%): C, 72.52; H, 4.01; N, 14.60.

3) 2-(2,4-Dichlorobenzylidenimino)-4-(4-chlorophenyl)-1-(3-trifluoromethylphenyl)-1H-pyrrole-3-carbonitrile; 5c

Yellow needle crystals; yield (49%); m.p.: 276˚C - 278˚C. **IR [KBr, cm^{-1}]**: 2933 (CH aromatic); 2850 (CH aliphatic); 2220 (C≡N); 1561 (C=N); 1024 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 7.30 (s, 1 H, CH-pyrrole); 7.33 - 7.36 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.42 - 7.51 (m, 3 H, 2,4-$(Cl)_2$-C_6H_3-$C_{3,5,6}$-H); 7.54 - 7.59 (m, 2 H, 3-CF_3-C_6H_4-$C_{4,6}$-H); 7.57 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.81 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.86 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 8.36 (s, 1 H, CH-benzylidinimine). **Anal. Calc**. (%) **for** $C_{25}H_{13}Cl_3F_3N_3$ (518.7): C, 57.88; H, 2.53; N, 8.10. **Found** (%): C, 57.65; H, 2.87; N, 8.59.

4) 2-(2,4-Dichlorobenzylidenimino)-4-(4-chlorophenyl)-1-(pyridin-3-yl)-1H-pyrrole-3-carbonitrile; 5d

Dark brown needle crystals; yield (85%); m.p.:240˚C - 242˚C. **IR [KBr, cm^{-1}]**: 3030 (CH aromatic); 2900 (CH aliphatic); 2199 (C≡N); 1620 (C=N); 1591 (C=C); 1094 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 452 ($M^{+\bullet}$+2, 1); 95 (100). **Anal**. **Calc**. (%) **for** $C_{23}H_{13}Cl_3N_4$ (451.7): C, 61.15; H, 2.90; N, 12.40. **Found** (%): C, 61.45; H, 3.02; N, 12.56.

3.1.5. General Procedure for Synthesis of Compounds 6a,b

An equimolar mixture of the selected 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and ethyl cyanoacetate (0.23 g, 0.1 mL, 2 mmol.) was heated under reflux in absolute ethanol (30 mL) for 8 h. The reaction mixture was allowed to cool and the product was collected and recrystallized from

glacial acetic acid.

1) 4-Amino-3-(4-chlorophenyl)-6-oxo-1-(3-trifluoromethylphenyl)-6,7-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile; 6a

Pale yellow needle crystals; yield (77%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3490, 3461 (br. OH tautomer); 3454, 3366, 3316 (NH_2, NH); 2960 (CH aromatic); 2200 (C≡N); 1660 (C=O); 1566 (C=C); 1022 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 4.93 (s, 2 H, NH_2, D_2O exchangeable); 7.08 (s, 1 H, CH-pyrrole); 7.34 - 7.38 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.48-7.62 (m, 2 H, 3-CF_3-C_6H_4-$C_{4,6}$-H); 7.64 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.86 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.90 (s, 1/2 H, NH, D_2O exchangeable); 8.45 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 10.28 (s, ½ H, OH tautomer, D_2O exchangeable). **Anal**. **Calc**. (%) **for** $C_{21}H_{12}ClF_3N_4O$ (428.8): C, 58.82; H, 2.82; N, 13.07. **Found** (%): C, 58.93; H, 2.88; N, 13.18.

2) 4-Amino-3-(4-chlorophenyl)-6-oxo-1-(pyridin-3-yl)-6,7-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile; 6b

Pale brown powder; yield (40%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3462, 3412 (br. OH tautomer); 3380, 3330, 3292, 3225 (NH_2, NH); 2920 (CH aromatic); 2206 (C≡N); 1680 (C=O); 1634 (C=N); 1525 (C=C); 1092 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 361 ($M^{+\bullet}$, 2); 360 ($M^{+\bullet}$-1, 3); 57 (100). **Anal**. **Calc**. (%) **for** $C_{19}H_{12}ClN_5O$ (361.8): C, 63.08; H, 3.34; N, 19.36. **Found** (%): C, 63.17; H, 3.76; N, 19.51.

3.1.6. General Procedure for Synthesis of Compounds 7a,b

Equimolar amounts of the appropriate 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and malononitrile (0.13 g, 0.1 mL, 2 mmol.) were heated under reflux in absolute ethanol (20 mL) for 14 h. The reaction mixture was allowed to cool and the product was collected, washed with ethanol and recrystallized from dioxane.

1) 4,6-Diamino-3-(4-chlorophenyl)-1-(3-trifluoromethylphenyl)-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile; 7a

Golden yellow needle crystals; yield (88%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3375, 3325 (NH_2); 2928 (CH aromatic); 2200 (C≡N); 1646 (C=N); 1560 (C=C); 1024 (*p*-Cl-phenyl).**^{1}H NMR(DMSO-d$_6$, δ ppm)**: 4.18 (s, 2 H, pyridine-C_4-NH_2, D_2O exchangeable); 5.19 (s, 2 H, pyridine-C_2-NH_2, D_2O exchangeable); 6.83 (s, 1 H, CH-pyrrole); 7.10 - 7.13 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.31 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.34 - 7.47 (m, 2 H, 3-CF_3-C_6H_4-$C_{4,6}$-H); 7.82 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.38 (s, 1 H, 3-CF_3-C_6H_4-C_2-H). **Anal**. **Calc**. (%) **for** $C_{21}H_{15}ClF_3N_5$ (429.8): C, 58.96; H, 3.06; N, 16.37. **Found** (%): C, 58.74; H, 3.21; N, 16.34.

2) 4,6-Diamino-3-(4-chlorophenyl)-1-(pyridin-3-yl)-1H-pyrrolo-[2,3-b]pyridine-5-carbonitrile; 7b

Buff powder; yield (58%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3428, 3364 (NH_2); 3066 (CH aromatic); 2198 (C≡N); 1638 (C=N); 1550 (C=C); 1092 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 363 ($M^{+\bullet}$+3, 2); 58 (100). **Anal**. **Calc**. (%) **for** $C_{19}H_{15}ClN_6$ (362.8): C, 63.25; H, 3.63; N, 23.29. **Found** (%): C, 63.92; H, 3.48; N, 23.20.

3.1.7. General Procedure for Synthesis of Compounds 8a,b

A mixture of the selected 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and hydroxylamine hydrochloride (0.14 g, 2 mmol.) in (30 mL) sodium ethoxide [prepared by dissolving sodium metal (0.06 g, 2 mmol.) in absolute ethanol (30 mL)] was refluxed for 12 h. Then the reaction was concentrated under reduced pressure and the residue was collected by filtration, washed thoroughly with water and recrystallized from ethanol/benzene mixture.

1) 4-(4-Chlorophenyl)-6-(3-trifluoromethylphenyl)-1,6-dihydropyrrolo[2,3-c]pyrazol-3-amine; 8a

Yellow powder; yield (75%); m.p.: 293˚C - 295˚C. **IR [KBr, cm^{-1}]**: 3418, 3290, 3240 (NH_2, NH); 3000, 2925 (CH aromatic); 1650 (C=N); 1560 (C=C); 1090 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 378 ($M^{+\bullet}$+2, 1); 377($M^{+\bullet}$+1, 1); 376 ($M^{+\bullet}$, 1); 58 (100). **Anal**. **Calc**. (%) **for** $C_{18}H_{12}ClF_3N_4$ (376.8): C, 57.38; H, 3.21; N, 14.87. **Found** (%): C, 57.45; H, 3.36; N, 14.92.

2) 4-(4-Chlorophenyl)-6-(pyridin-3-yl)-1,6-dihydropyrrolo[2,3-c]pyrazol-3-amine; 8***b***

Pale brown powder; yield (64%); m.p.: > 300˚C. **IR [KBr, cm^{-1}]**: 3428, 3332, 3270, 3214, 3132 (NH_2, NH), 3040 (CH aromatic); 1636 (C=N); 1550 (C=C); 1094 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 5.27 (s, 2 H, NH_2, D_2O exchangeable); 6.77 (s, 1 H, CH-pyrrole); 7.33 (d, 2 H, *J* = 7.8 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.56 - 7.70 (m, 3 H, pyridyl-$C_{4,5,6}$-H); 7.87 (d, 2 H, *J* = 7.8 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.92 (s, 1 H, pyridyl-C_2-H); 8.06 (s, 1 H, NH, D_2O exchangeable). **Anal**. **Calc**. (%) **for** $C_{16}H_{12}ClN_5$ (309.8): C, 62.04; H, 3.90; N, 22.61 **Found** (%): C, 62.10; H, 3.93; N, 22.69.

3.1.8. General Procedure for Synthesis of Compounds 9a-d

The appropriate compound **4a,b** (2 mmol.) was refluxed with equimolar amount of urea or thiourea (2 mmol.) in absolute ethanol (20 mL) containing sodium ethoxide [prepared by dissolving sodium metal (0.03 g, 2 mmol.) in absolute ethanol (20 mL)] for 10 h. The reaction was allowed to cool and the solid product was filtered and washed with ethanol.

1) 1-[4-(4-Chlorophenyl)-3-cyano-1-(3-trifluoromethylphenyl)-1H-pyrrol-2-yl]urea; 9a

Pale yellow crystals; gl. acetic; yield (80%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3324, 3248, 3164 (NH_2, NH); 3092 (CH aromatic); 2225 (C≡N); 1700 (C=O); 1562 (C=C); 1024 (*p*-Cl-phenyl);); **MS** m/z (relative intensity %): 405 ($M^{+\bullet}$+1, 0.2); 404 ($M^{+\bullet}$, 0.2); 57 (100). **Anal**. **Calc**. (%) **for** $C_{19}H_{12}ClF_3N_4O$ (404.8): C, 56.38; H, 2.99; N, 13.84. **Found** (%): C, 56.44; H, 3.05; N, 13.96.

2) 1-[4-(4-Chlorophenyl)-3-cyano-1-(pyridin-3-yl)-1H-pyrrol-2-yl]urea; 9b

Buff powder; gl. acetic; yield (67%); m.p.: 324˚C - 326˚C. **IR [KBr, cm^{-1}]**: 3375, 3310, 3244, 3200 (NH_2, NH); 3025 (CH aromatic); 2225 (C≡N); 1680 (C=O); 1636 (C=N);1456 (C=C); 1100 (*p*-Cl phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 5.46 (s, 2 H, NH_2, D_2O exchangeable); 6.70 (s, 1 H, CH-pyrrole); 7.30 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.57 - 7.65 (m, 3 H, pyridyl-$C_{4,5,6}$-H); 7.84 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.04 (s, 1 H, NH, D_2O exchangeable); 8.48 (s, 1 H, pyridyl-C_2-H). **^{13}C NMR (DMSO-d$_6$, δ ppm)**: 106.2 (pyrrole-C_3); 114 (C≡N); 117 (pyrrole-C_5); 119 (pyrrole-C_2); 124 (pyrrole-C_4); 124.4 (pyridyl-C_5); 126.7 (pyridyl-C_6); 127.1 (4-Cl-C_6H_4-$C_{2,6}$); 127.6 (4-Cl-C_6H_4-$C_{3,5}$); 130.8 (4-Cl-C_6H_4-C_4); 131.6 (4-Cl-C_6H_4-C_1); 133.5 (pyridyl-C_1); 138.9 (pyridyl-C_2); 148.4 (pyridyl-C_4); 159.8 (C=O) of amide. **Anal**. **Calc**. (%) for $C_{17}H_{12}ClN_5O$ (337.8): C, 60.45; H, 3.58; N, 20.73. **Found** (%): C, 60.71; H, 3.63; N, 20.78.

3) 1-[4-(4-Chlorophenyl)-3-cyano-1-(3-trifluoromethylphenyl)-1H-pyrrol-2-yl]thiourea; 9c

Yellow powder; petroleum ether 60/80; yield (54%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3413, 3250, 3183 (NH_2, NH); 2933 (CH aromatic); 2259 (C≡N); 1562 (C=C); 1562, 1416, 1100, 922 (I, II, III, IV bands N-C=S); 1025 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 5.47 (s, 2 H, NH_2, D_2O exchangeable); 7.05 (s, 1 H, CH-pyrrole); 7.12-7.15 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.30 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.34-7.47 (m, 2 H, 3-CF_3-C_6H_4-$C_{4,6}$-H); 7.82 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.40 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 10.62 (s, 1 H, NH, D_2O exchangeable). **Anal**. **Calc**. (%) **for** $C_{19}H_{12}ClF_3N_4S$ (420.8): C, 54.23; H, 2.87; N, 13.31. **Found** (%): C, 54.27; H, 2.93; N, 13.56.

4) 1-[4-(4-Chlorophenyl)-3-cyano-1-(pyridin-3-yl)-1H-pyrrol-2-yl]thiourea; 9d

Pale browncrystals; dioxane; yield (89%); m.p.: 334˚C - 336˚C. **IR [KBr, cm^{-1}]**: 3424, 3380, 3330 (NH_2, NH); 3020 (CH aromatic); 2196 (C≡N); 1628 (C=N); 1552 (C=C); 1500, 1280, 1098, 1006 (I, II, III, IV bands N-C=S); 1110 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 355 ($M^{+\bullet}$+2, 0.5); 353 ($M^{+\bullet}$, 1); 352 ($M^{+\bullet}$−1, 1); 57 (100). **Anal**. **Calc**. (%) **for** $C_{17}H_{12}ClN_5S$ (353.8): C, 57.71; H, 3.42; N, 19.79. **Found** (%): C, 57.80; H, 3.45; N, 19.88.

3.1.9. General Procedure for Synthesis of Compounds 10a-d

Method 1:

A mixture of the selected 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) was refluxed and urea (0.12 g, 2 mmol.) and/or thiourea (0.15 g, 2 mmol.) was refluxed for 12 h. in a mixture of glacial acetic acid and HCl (20 mL) (3:1). The reaction was allowed to cool, filtered and washed with ethanol to yield the target compounds **10a-d** in an average yield of 82%.

Method 2:

The selected urea or thiourea derivative **9a-d** (2 mmol.) was refluxed in pyridine (10 mL) for 16 h. The solvent was evaporated under reduced pressure and the solid obtained was collected to yield the target compounds **10a-d** in an average yield of 63%.

1) 4-Amino-5-(4-chlorophenyl)-7-(3-trifluoromethylphenyl)-1H-pyrrolo[2,3-d]pyrimidine-2(7H)-one; 10a

Light brown crystals; Ethanol/Benzene; yield (73%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3450 (br. OH tautomer); 3356, 3211 (NH_2, NH); 3080 (CH aromatic); 1654 (C=O); 1458 (C=C); 1100 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 406 ($M^{+\bullet}$+2, 1); 405 ($M^{+\bullet}$+1, 1); 404 ($M^{+\bullet}$, 1); 61 (100). **Anal**. **Calc**. (%) for $C_{19}H_{12}ClF_3N_4O$ (404.8): C, 56.38; H, 2.99; N, 13.84. **Found** (%): C, 56.43; H, 3.07; N, 13.93.

2) 4-Amino-5-(4-chlorophenyl)-7-(pyridin-3-yl)-1H-pyrrolo[2,3-d]pyrimidine-2(7H)-one; 10b

Pale brownpowder; dioxane; yield (40%); m.p.: 286˚C - 288˚C. **IR [KBr, cm^{-1}]**: 3480 (br. OH tautomer); 3420, 3223 (NH_2, NH); 3100 (CH aromatic); 1690 (C=O); 1095 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**:

4.15 (s, 2 H, NH_2, D_2O exchangeable); 4.94 (s, 1/2 H, NH, D_2O exchangeable); 7.39 - 7.41 (m, 3 H, pyridyl-$C_{4,5,6}$-H); 7.42 (s, 1 H, CH-pyrrole); 7.50 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.83 (s, 1/2 H, OH, tautomer, D_2O exchangeable); 8.05 (s, 1 H, pyridyl-C_2-H); 8.17 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H). **Anal**. **Calc**. (%) **for** $C_{17}H_{12}ClN_5O$ (337.8): C, 60.45; H, 3.58; N, 20.73. **Found** (%): C, 60.62; H, 3.60; N, 20.81.

3) 4-Amino-5-(4-chlorophenyl)-7-(3-trifluoromethylphenyl)-1H-pyrrolo[2,3-d]pyrimidine-2(7H)-thione; 10c

Pale yellowpowder; Ethanol; yield (65%); m.p.: >360˚C. **IR [KBr, cm^{-1}]**: 3367, 3265 (NH_2, NH); 3164 (CH aromatic); 1480, 1328, 1120, 1097 (I, II, III, IV bands N-C=S); 1080 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 4.76 (s, 1 H, NH, D_2O exchangeable); 6.37 (s, 2 H, NH_2, D_2O exchangeable); 6.85 (d, 1 H, *J* = 7.2 Hz, 3-CF_3-C_6H_4-C_6-H); 6.95 (d, 2 H, *J* = 8.3 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.00 (s, 1 H, CH-pyrrole); 7.25 - 7.30 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.64 (d, 2 H, *J* = 8.3 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.08 - 8.12 (m, 2 H, 3-CF_3-C_6H_4-$C_{2,4}$-H). **^{13}C NMR(DMSO-d$_6$, δ ppm)**: 107.8 (pyrrolopyrimidine C_{4a}); 113 (3-CF_3-C_6H_4-C_2); 116.6 (pyrrolopyrimidine C_6); 120 (pyrrolopyrimidine C_{7a}); 121.9 (3-CF_3-C_6H_4-C_4); 124.1 (CF_3); 124.8 (3-CF_3-C_6H_4-C_6); 126 (pyrrolopyrimidine C_5); 128.9 (4-Cl-C_6H_4-$C_{2,6}$); 129.8 (4-Cl-C_6H_4-$C_{3,5}$-H); 130.9 (3-CF_3-C_6H_4-C_5); 131.04 (3-CF_3-C_6H_4-C_3); 131.08 (4-Cl-C_6H_4-C_4); 135.8 (4-Cl-C_6H_4-C_1); 145 (3-CF_3-C_6H_4-C_1); 157 (pyrrolopyrimidine C_4); 185 (C=S). **Anal**. **Calc**. (%) **for** $C_{19}H_{12}ClF_3N_4S$ (420.8): C, 54.23; H, 2.87; N, 13.31. **Found** (%): C, 54.27; H, 2.91; N, 13.46.

4) 4-Amino-5-(4-chlorophenyl)-7-(pyridin-3-yl)-1H-pyrrolo[2,3-d]pyrimidine-2(7H)-thione; 10d

Pale brown powder; Ethanol; yield (83%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3428, 3350, 3220 (NH_2, NH); 3080 (CH aromatic); 1624 (C=N); 1404, 1316, 1150, 1000 (I, II, III, IV bands N-C=S); 1100 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 355 ($M^{+\bullet}$+2, 0.6); 354 ($M^{+\bullet}$+1, 1); 353 ($M^{+\bullet}$, 2); 58 (100). **Anal**. **Calc**. (%) **for** $C_{17}H_{12}ClN_5S$ (353.8): C, 57.71; H, 3.42; N, 19.79. **Found** (%): C, 57.80; H, 3.51; N, 19.84.

3.1.10. General Procedure for Synthesis of Compounds 11a,b

A mixture of the appropriate 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and phenyl isothiocyanate (0.27 g, 0.24 mL, 2 mmol.) was refluxed for 7 h in absolute ethanol (30 mL) and the solid product was filtered and washed with ethanol.

1) 1-[4-(4-Chlorophenyl)-3-cyano-1-(3-trifluoromethylphenyl)-1H-pyrrol-2-yl]-3-phenylthiourea; 11a

Yellow needle crystals; gl.acetic; yield (57%); m.p.: >360˚C. **IR [KBr, cm^{-1}]**: 3372, 3286 (NH); 3050 (CH aromatic); 2200 (C≡N); 1562 (C=C); 1418, 1282, 1170, 1020 (I, II, III, IV bands N-C=S); 1098 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 6.90 (s, 1 H, CH-pyrrole); 7.10 - 7.13 (m, 3 H, C_6H_5-$C_{3,4,5}$-H); 7.30 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.34-7.39 (m, 3 H, 3-CF_3-C_6H_4-$C_{4,5,6}$-H); 7.47 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.80 (d, 2 H, *J* = 7.2 Hz, C_6H_5-$C_{2,6}$-H); 7.83 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 8.70 (s, 1 H, pyrrole-C_2-NH, D_2O exchangeable); 9.59 (s, 1 H, NH, D_2O exchangeable). **Anal**. **Calc**. (%) **for** $C_{25}H_{16}ClF_3N_4S$ (496.9): C, 60.42; H, 3.25; N, 11.27. **Found** (%): C, 60.44; H, 3.35; N, 11.31.

2) 1-[4-(4-Chlorophenyl)-3-cyano-1-(pyridin-3-yl)-1H-pyrrol-2-yl]-3-phenylthiourea; 11b

Buff crystals; DMF; yield (70%); m.p.: 288˚C - 290˚C. **IR [KBr, cm^{-1}]**: 3374, 3326, 3260, 3200 (NH); 3090 (CH aromatic); 2206 (C≡N); 1640 (C=N); 1566 (C=C); 1420, 1396, 1250, 1110 (I, II, III, IV bands N-C=S); 1098 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 429 ($M^{+\bullet}$, 2); 83 (100). **Anal**. **Calc**. (%) **for** $C_{23}H_{16}ClN_5S$ (429.9): C, 64.25; H, 3.75; N, 16.29. **Found** (%): C, 64.29; H, 3.77; N, 16.32.

3.1.11. General Procedure for Synthesis of Compounds 12a,b

Method 1:

A mixture of the appropriate 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and phenyl isothiocyanate (0.27 g, 0.24 mL, 2 mmol.) was refluxed in pyridine (15 mL) for 10 h and the solid product was filtered, washed with ethanol to yield the target compounds **12a,b** in an average yield of 53%.

Method 2:

The selected phenyl thiourea derivatives **11a,b** was refluxed in pyridine (10 mL) for 18 h. The solvent was evaporated under reduced pressure to yield the target compounds **12a,b** in an average yield of 48%.

1) 5-(4-Chlorophenyl)-4-imino-3-phenyl-7-(3-trifluoromethylphenyl)-3,4-dihydro-1H-pyrrolo[2,3-d]pyrimi dine-2(7H)-thione; 12a

Light brown crystals; dioxane; yield (68%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3190 (NH); 3050 (CH aromatic); 1546 (C=C); 1434, 1332, 1180, 1020 (I, II, III, IV bands N-C=S); 1100 (*p*-Cl-phenyl); **MS** m/z (relative intensi-

ty %): 496 ($M^{+\bullet}$, 1); 140 (100). **Anal**. **Calc**. (%) **for** $C_{25}H_{16}ClF_3N_4S$ (496.9): C, 60.42; H, 3.25; N, 11.27. **Found** (%): C, 60.51; H, 3.28; N, 11.29.

2) 5-(4-Chlorophenyl)-4-imino-3-phenyl-7-(pyridin-3-yl)-3,4-dihydro-1H-pyrrolo[2,3-d]pyrimidine-2(7H)-thione; 12b

Dark grey powder; dioxane; yield (59%); m.p.: > 300˚C. **IR [KBr, cm^{-1}]**: 3317, 3191 (NH); 3020 (CH aromatic); 1625 (C=N); 1520 (C=C); 1406, 1250, 1134, 1026 (I, II, III, IV bands N-C=S); 1080 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 5.30 (s, 1 H, NH, D_2O exchangeable); 6.63 (s, 1 H, CH-pyrrole); 6.85 - 7.05 (m, 3 H, C_6H_5-$C_{3,4,5}$-H); 7.30 - 7.50 (m, 2 H, C_6H_5-$C_{2,6}$-H); 7.56 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.62 - 7.78 (m, 2 H, pyridyl-$C_{5,6}$-H); 7.94 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.99 - 8.03 (m, 2 H, pyridyl-$C_{2,4}$-H); 10.58 (s, 1 H, imine NH, D_2O exchangeable). **Anal**. **Calc**. (%) **for** $C_{23}H_{16}ClN_5S$ (429.9): C, 64.25; H, 3.75; N, 16.29. **Found** (%): C, 64.29; H, 3.80; N, 16.36.

3.1.12. General Procedure for Synthesis of Compounds 13a,b

A mixture of the appropriate 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and triethyl orthoformate (0.29 g, 0.33 mL, 2 mmol.) in acetic anhydride (25 mL) was heated under reflux for 6 h. The reaction mixture was concentrated to the minimum and left to cool. The obtained product was collected washed with ethanol and recrystallized from dimethylformamide.

1) Ethyl N-4-(4-chlorophenyl)-3-cyano-1-(3-trifluoromethylphenyl)-1H-pyrrol-2-ylformimidate; 13a

Pale yellow crystals; yield (67%); m.p.: 298˚C - 300˚C. **IR [KBr, cm^{-1}]**: 3100 (CH aromatic); 2900 (CH-aliphatic); 2190 (C≡N); 1620 (C=N); 1560 (C=C); 1270, 1025 (C-O-C); 1090 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 1.17 (t, 3 H, *J* = 6.8 Hz, CH_2CH_3); 4.05 - 4.10 (m, 2 H, CH_2CH_3); 6.80 (s, 1 H, CH- pyrrole); 7.15 - 7.18 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.30 - 7.33 (m, 2 H, 3-CF_3-C_6H_4-$C_{4,6}$-H); 7.35 (s, 1 H, N=CH); 7.51(d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.81 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.36 (s, 1 H, 3-CF_3-C_6H_4-C_2-H). **Anal**. **Calc**. (%) **for** $C_{21}H_{15}ClF_3N_3O$ (417.8): C, 60.37; H, 3.62; N, 10.06. **Found** (%): C, 60.41; H, 3.65; N, 10.12.

2) Ethyl N-4-(4-chlorophenyl)-3-cyano-1-(pyridin-3-yl)-1H-pyrrol-2-ylformimidate; 13b

Dark brown needle crystals; yield (49%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3178 (CH aromatic); 2923, 2860 (CH-aliphatic); 2198 (C≡N); 1630 (C=N); 1557 (C=C); 1280, 1023 (C-O-C); 1023 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 352 ($M^{+\bullet}$+2, 0.4); 351 ($M^{+\bullet}$+1, 0.5); 350 ($M^{+\bullet}$, 0.4); 349 ($M^{+\bullet}$−1, 0.4); 58 (100). **Anal**. **Calc**. (%) **for** $C_{19}H_{15}ClN_4O$ (350.8): C, 65.05; H, 4.31; N, 15.97. **Found** (%): C, 65.10; H, 4.37; N, 15.99.

3.1.13. General Procedure for Synthesis of Compounds 14a,b

Method 1:

The appropriate 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) was refluxed in excess formamide (30 mL) for 10 h. The reaction mixture was concentrated to the minimum and left to cool then triturated with glacial acetic acid to yield the target compounds **14a,b** in an average yield of 66%.

Method 2:

The selected ethyl N-1-(substitutedaryl)-4-(4-chlorophenyl)-3-cyano-1H-pyrrol-2-ylformimidate **13a,b** (2 mmol.) was stirred in (100 mL) of methanolic ammonia solution [methanol: ammonia (2:1)] at room temperature for 7 h. The separated solid was then collected to yield the target compounds **14a,b** in an average yield of 41%.

1) 5-(4-Chlorophenyl)-7-(3-trifluoromethylphenyl)-7H-pyrrolo[2,3-d]pyrimi-din-4-amine; 14a

Pale yellow powder; gl. acetic; yield (51%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3408, 3350, 3240 (NH_2); 3020 (CH aromatic); 1525 (C=C); 1098 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 390 ($M^{+\bullet}$+2, 2); 389 ($M^{+\bullet}$+1, 1); 388 ($M^{+\bullet}$, 1); 387 ($M^{+\bullet}$−1, 2); 57 (100). **Anal**. **Calc**. (%) **for** $C_{19}H_{12}ClF_3N_4$ (388.8): C, 58.70; H, 3.11; N, 14.41. **Found** (%): C, 58.73; H, 3.18; N, 14.49.

2) 5-(4-Chlorophenyl)-7-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine; 14b

Dark brown powder; gl. acetic; yield (67%); m.p.: 320˚C - 322˚C. **IR [KBr, cm^{-1}]**: 3436, 3382 (NH_2); 3092 (CH aromatic); 1550 (C=N); 1450 (C=C); 1100 (*p*-Cl phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 7.38 (s, 2 H, NH_2, D_2O exchangeable); 7.41 - 7.50 (m, 2 H, pyridyl-$C_{4,5}$-H); 7.69 (s, 1 H, CH-pyrrole); 7.78 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.91-8.10 (m, 3 H, pyridyl-C_6-H & 4-Cl-C_6H_4-$C_{3,5}$-H); 8.87 (s, 1 H, pyridyl-C_2-H); 9.06 (s, 1 H, pyrimidine-C_2-H). **Anal**. **Calc**. (%) **for** $C_{17}H_{12}ClN_5$ (321.8): C, 63.46; H, 3.76; N, 21.77. **Found** (%): C,

63.53; H, 3.80; N, 21.80.

3.1.14. General Procedure for Synthesis of Compounds 15a,b

Method 1:

Equimolar amounts of the selected of 1-(substituted aryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and N,N-dimethylformamide-dimethylacetal (0.24 g, 0.27 mL, 2 mmol.) in xylene (20 mL) were refluxed for 6 h. The reaction mixture was concentrated under reduced pressure and the obtained products were filtered, washed with ethanol to yield the target compounds **15a,b** in an average yield of 45%.

Method 2:

The appropriate ethyl 1-(substitutedaryl)-N-4-(4-chlorophenyl)-3-cyano-1H-pyrrol-2-ylformimidate **13a,b** (2 mmol.) and dimethylamine (0.09 g, 0.1 mL, 2 mmol.) were stirred for 2 h in absolute ethanol (50 mL). The obtained product was filtered off, washed with ethanol to yield the target products **15a,b** in an average yield of 57%.

1) N'-[4-(4-Chlorophenyl)-3-cyano-1-(3-trifluoromethylphenyl)-1H-pyrrol-2-yl]-N,N-dimethylformimidamide; 15a

Faint yellow crystals; Ethanol/Benzene.; yield (67%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3040 (CH aromatic); 2900, 2850 (CH-aliphatic); 2220 (C≡N); 1648 (C=N); 1560 (C=C); 1024 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 418 ($M^{+\bullet}$+2, 0.6); 415 ($M^{+\bullet}$−1, 0.4); 284 (100). **Anal**. **Calc**. (%) **for** $C_{21}H_{16}ClF_3N_4$ (416.8): C, 60.51; H, 3.87; N, 13.44. **Found** (%): C, 60.55; H, 3.93; N, 13.51.

2) N'-[4-(4-Chlorophenyl)-3-cyano-1-(pyridin-3-yl)-1H-pyrrol-2-yl]-N,N-dimethylformimidamide; 15b

Buff crystals; Ethanol/Benzene.; yield (59%); m.p.: 288˚C - 290˚C. **IR [KBr, cm^{-1}]**: 3030 (CH aromatic); 2930, 2840 (CH-aliphatic); 2202 (C≡N); 1648 (C=N); 1564 (C=C); 1090 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d_6, δ ppm)**: 3.80 (s, 6 H, two CH_3); 7.30 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.45-7.65 (m, 3 H, CH-pyrrole, pyridyl-$C_{5,6}$-H); 7.82 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.98 (s, 1 H, N=CH); 8.21 (d, 1 H, *J* = 6.7 Hz, pyridyl-C_4-H); 8.41 (s, 1 H, pyridyl-C_2-H). **Anal**. **Calc**. (%) **for** $C_{19}H_{16}ClN_5$ (349.8): C, 65.24; H, 4.61; N, 20.02. **Found** (%): C, 65.28; H, 4.72; N, 20.10.

3.1.15. General Procedure for Synthesis of Compounds 16a,b

A mixture of the selected 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and *p*-toluene sulphonyl chloride (0.38 g, 2 mmol.) was refluxed for 7 h. in toluene (15 mL) containing drops of TEA. The solid obtained was filtered off, washed with ethanol and recrystallized from ethanol/benzene mixture.

1) N-[4-(4-Chlorophenyl)-3-cyano-1-(3-trifluoromethylphenyl)-1H-pyrrol-2-yl)-4-methylbenzenesulfonamide; 16a

Orange yellow crystals; yield (59%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3230, 3198 (NH); 3000 (CH aromatic); 2921, 2858 (CH-aliphatic); 2260 (C≡N); 1522 (C=C); 1452, 1350, 1120 (SO_2); 1035 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 516 ($M^{+\bullet}$+1, 2); 57 (100). **Anal**. **Calc**. (%) **for** $C_{25}H_{17}ClF_3N_3O_2S$ (515.9): C, 58.20; H, 3.32; N, 8.14. **Found** (%): C, 58.26; H, 3.37; N, 8.17.

2) N-[4-(4-Chlorophenyl)-3-cyano-1-(pyridin-3-yl)-1H-pyrrol-2-yl]-4-methylbenzenesulfonamide; 16b

Buff powder**;** yield (63%); m.p.: >360˚C. **IR [KBr, cm^{-1}]**: 3310, 3180 (NH); 3050 (CH aromatic); 2923, 2858 (CH-aliphatic); 2209 (C≡N); 1543 (C=C); 1420, 1300, 1177 (SO_2); 1026 (*p*-Cl phenyl). **^{1}H NMR (DMSO-d_6, δ ppm)**: 2.29 (s, 3 H, CH_3); 7.11 (d, 2 H, *J* = 8.1 Hz, 4-CH_3-C_6H_4-$C_{3,5}$-H); 7.18 (s, 1 H, CH-pyrrole); 7.38 - 7.42 (m, 4 H, 4-Cl-C_6H_4-$C_{2,6}$-H & 4-CH_3-C_6H_4-$C_{2,6}$-H); 7.48 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.60 - 7.85 (m, 3 H, pyridyl-$C_{4,5,6}$-H); 8.07 (s, 1 H, pyridyl-C_2-H); 9.40 (s, 1 H, NH, D_2O exchangeable). **^{13}C (DMSO-d_6)**: 20.7 (CH_3); 109 (pyrrole-C_3); 114 (C≡N); 117 (pyrrole-C_5); 119 (pyrrole-C_2); 124 (pyrrole-C_4); 124.4 (pyridyl-C_5); 125.4 (pyridyl-C_6); 128 (4-CH_3-C_6H_4-$C_{2,6}$); 128.9 (4-Cl-C_6H_4-$C_{2,6}$); 131 (4-Cl-C_6H_4-$C_{3,5}$& 4-CH_3-C_6H_4-$C_{3,5}$); 133 (4-Cl-C_6H_4-C_6); 134 (4-Cl-C_6H_4-C_1); 135 (pyridyl-C_1); 137.8 (4-CH_3-C_6H_4-C_1); 139 (4-CH_3-C_6H_4-C_4); 143.9 (pyridyl-C_2); 145.2 (pyridyl-C_4). **Anal**. **Calc**. (%) **for** $C_{23}H_{17}ClN_4O_2S$ (448.9): C, 61.54; H, 3.82; N, 12.48. **Found** (%): C, 61.58; H, 3.88; N, 12.51.

3.1.16. General Procedure for Synthesis of Compounds 17a,b

The selected compound **4a,b** (2 mmol.) was stirred at room temperature for 3 h. inconc. sulfuric acid (15 mL) then poured drop by drop on to crushed ice. The reaction mixture was neutralized with ammonium hydroxide

and the obtained product was filtered, washed thoroughly with water, left to dry and recrystallized from ethanol.

1) 2-Amino-4-(4-chlorophenyl)-1-(3-trifluoromethylphenyl)-1H-pyrrole-3-carboxamide; 17a

Brown needle crystals; yield (43%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3390, 3167 (NH_2); 3020 (CH aromatic); 1683 (C=O); 1110 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 6.37 (s, 2 H, NH_2, D_2O exchangeable); 6.94 (d, 1 H, *J* = 7.2 Hz, 3-CF_3-C_6H_4-C_6-H); 7.00 (s, 1 H, CH-pyrrole); 7.25 - 7.30 (m, 2 H, 3-CF_3-C_6H_4-$C_{4,5}$-H); 7.34 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.63 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.11 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 8.60 (s, 2 H, $CONH_2$, D_2O exchangeable). **Anal**. **Calc**. (%) **for** $C_{18}H_{13}ClF_3N_3O$ (379.8): C, 56.93; H, 3.45; N, 11.06. **Found** (%): C, 56.97; H, 3.52; N, 11.13.

2) 2-Amino-4-(4-chlorophenyl)-1-(pyridin-3-yl)-1H-pyrrol-3-carboxamide; 17b

Dark brown powder; yield (65%); m.p.: 305˚C - 307˚C. **IR [KBr, cm^{-1}]**: 3430, 3292, 3182 (NH_2); 3015 (CH aromatic); 1672 (C=O); 1620 (C=N); 1512 (C=C); 1069 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 314 ($M^{+\bullet}$+2, 1); 313 ($M^{+\bullet}$+1, 2); 312 ($M^{+\bullet}$, 0.3); 197 (100). **Anal**. **Calc**. (%) **for** $C_{16}H_{13}ClN_4O$ (312.8): C, 61.44; H, 4.19; N, 17.91. **Found** (%): C, 61.47; H, 4.23; N, 17.96.

3.1.17. General Procedure for Synthesis of Compounds 18a,b

Method 1:

The selected 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) was refluxed for 9 h. in excess formic acid 80% (30 mL). The reaction mixture was then concentrated and the obtained product was filtered, washed with ethanol to yield the target compounds **18a,b** in an average yield of 52%.

Method 2:

The selected 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carboxamide **17a,b** (2 mmol.) was refluxed in excess formamide (30 mL) for 8 h. The reaction mixture was concentrated to yield the target compounds **18a,b** in an average yield of 67%.

1) 5-(4-Chlorophenyl)-7-(3-trifluoromethylphenyl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one; 18a

Faint yellow powder; Ethanol; yield (48%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3386 (br. OH, tautomer); 3280 (NH); 3000 (CH aromatic); 1680 (C=O); 1470 (C=C); 1090 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 5.27 (s, 1/2 H, NH, D_2O exchangeable); 6.76 (s, 1 H, CH-pyrrole); 6.80 - 6.90 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 6.98 (d, 1 H, *J* = 7.2 Hz, 3-CF_3-C_6H_4-C_6-H); 7.33 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.54 (d, 1 H, *J* = 6.9 Hz, 3-CF_3-C_6H_4-C_4-H); 7.65 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H);7.88 (s, 1 H, CH-pyrimidine); 7.91 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 8.06 (s, 1/2 H, OH tautomer, D_2O exchangeable). **Anal**. **Calc**. **(%) for** $C_{19}H_{11}ClF_3N_3O$ (389.8): C, 58.55; H, 2.84; N, 10.78. **Found (%)**: C, 58.58; H, 2.89; N, 10.81.

2) 5-(4-Chlorophenyl)-7-(pyridin-3-yl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one; 18b

Grey powder; Ethanol; yield (54%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3429 (br. OH tautomer); 3200 (NH); 3048 (CH aromatic); 1670 (C=O); 1598 (C=C); 1098 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 324 ($M^{+\bullet}$+2, 0.1); 323 ($M^{+\bullet}$+1, 0.1); 78 (100). **Anal**. **Calc. (%)** for $C_{17}H_{11}ClN_4O$ (322.7): C, 63.26; H, 3.44; N, 17.36. **Found (%)**: C, 63.31; H, 3.54; N, 17.41.

3.1.18. General Procedure for Synthesis of Compounds 19a,b

The selected 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrol-3-carboxamide **17a,b** (2 mmol.) was refluxed in excess thionyl chloride (15 mL) for 6 h. The reaction mixture was evaporated under reduced pressure. The residue was triturated with ethanol, filtered then recrystallized from glacial acetic acid.

1) 7-(4-Chlorophenyl)-5-(3-trifluoromethylphenyl)-1H-pyrrolo[3,2-d]1,2,6-thiadiazine-2,4(1H,3H)-dione; 19a

Faint orange powder; yield (48%); m.p.: 294˚C - 296˚C. **IR [KBr, cm^{-1}]**: 3181 (NH); 3070 (CH aromatic); 1706 (C=O); 1520 (C=C); 1139 (S=O); 1050 (*p*-Cl-phenyl).**^{1}H NMR(DMSO-d$_6$, δ ppm):** 4.20 (s, 1 H, NH, D_2O exchangeable); 7.03 (s, 1 H, CH-pyrrole); 7.10 - 7.20 (m, 3 H, 3-CF_3-C_6H_4-$C_{4,5,6}$-H); 7.37 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.68 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.92 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 8.06 (s, 1 H, NH, D_2O exchangeable); **MS** m/z (relative intensity %): 427 ($M^{+\bullet}$+2, 0.1); 426 ($M^{+\bullet}$+1, 0.1); 425 ($M^{+\bullet}$, 0.2); 424 ($M^{+\bullet}$−1, 52); 229 (100). **Anal**. **Calc**. **(%)** for $C_{18}H_{11}ClF_3N_3O_2S$ (425.8): C, 50.77; H, 2.60; N, 9.87. **Found (%)**: C, 50.81; H, 2.68; N, 9.91.

2) 7-(4-Chlorophenyl)-5-(pyridin-3-yl)-1H-pyrrolo[3,2-d]1,2,6-thiadiazin-2,4(1H,3H)-dione; 19b

Dark brown powder; yield (53%); m.p.: 310˚C - 312˚C. **IR [KBr, cm^{-1}]**: 3354 (NH); 3090 (CH aromatic); 1690 (C=O); 1650 (C=N); 1524 (C=C); 1112 (S=O); 1046 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 360

($M^{+\bullet}$+2, 2); 358 ($M^{+\bullet}$, 2); 71 (100). **Anal**. **Calc**. **(%)** for$C_{16}H_{11}ClN_4O_2S$(358.8): C, 53.56; H, 3.09; N, 15.61. **Found** (%): C, 53.58; H, 3.12; N, 15.67.

3.1.19. General Procedure for Synthesis of Compounds 20a,b

The selected 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carboxamide **17a,b** (2 mmol.) was refluxed in excess acetic anhydride (15 mL) for 10 h. The reaction mixture was concentrated to the minimum. The solid product was collected, washed with ethanol then recrystallized from dioxane.

1) 5-(4-Chlorophenyl)-2-methyl-7-(3-trifluoromethylphenyl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one; 20a

Faint brown needle crystals; yield (51%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3418 (br. OH tautomer); 3150 (NH); 3060 (CH aromatic); 1616 (C=N); 1539 (C=C); 1095 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d_6, δ ppm)**: 2.73 (s, 3 H, CH_3); 7.04 (s, 1 H, CH-pyrrole); 7.31 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.42-7.54 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.60 (d, 1 H, *J* = 7.2 Hz, 3-CF_3-C_6H_4-C_6-H); 7.69 (d, 1 H, *J* = 6.9 Hz, 3-CF_3-C_6H_4-C_4-H); 7.81 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.96 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 9.63 (s, 1/2 H, NH, D_2O exchangeable); 11.50 (s, 1/2 H, OH tautomer, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{20}H_{13}ClF_3N_3O$ (403.8): C, 59.49; H, 3.25; N, 10.41. **Found (%)**: C, 59.53; H, 3.31; N, 10.48.

2) 5-(4-Chlorophenyl)-2-methyl-7-(pyridin-3-yl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one; 20b

Dark brown needle crystals; yield (47%); m.p.: 272˚C - 274˚C. **IR [KBr, cm^{-1}]**: 3140 (NH); 3030 (CH aromatic); 2890 (CH aliphatic); 1652 (C=O); 1610 (C=N); 1107 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d_6, δ ppm)**: 2.07 (s, 3 H, CH_3); 7.30 - 7.40 (m, 2 H, pyridyl-$C_{5,6}$-H); 7.58 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.64 (s, 1 H, CH-pyrrole); 7.95 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.99 - 8.16 (m, 2 H, pyridyl-$C_{2,4}$-H); 9.29 (s, 1/2 H, NH, D_2O exchangeable); 10.99 (s, 1/2 H, OH tautomer, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{18}H_{13}ClN_4O$ (336.8): C, 64.19; H, 3.89; N, 16.64. **Found (%)**: C, 64.22; H, 3.91; N, 16.65.

3.1.20. General Procedure for Synthesis of Compounds 21a,b

The selected 7-(substitutedaryl)-5-(4-chlorophenyl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one **18a,b** (2 mmol.) was refluxed in excess $POCl_3$ (15 mL) for 18 h. The reaction mixture was allowed to cool then poured on to crushed ice then alkalinized with sodium bicarbonate till pH 10. The obtained product was filtered, washed with water then recrystallized from glacial acetic acid.

1) 4-Chloro-5-(4-chlorophenyl)-7-(3-trifluoromethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine; 21a

Yellow crystals;yield (71%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 2924 (CH aromatic); 1620 (C=N); 1542 (C=C); 1100 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 408 ($M^{+\bullet}$+1, 0.2); 407 ($M^{+\bullet}$, 0.2); 406 ($M^{+\bullet}$−1, 0.2); 405 ($M^{+\bullet}$−2) (0.2); 58 (100). **Anal**. **Calc**. **(%)** for $C_{19}H_{10}Cl_2F_3N_3$ (408.2): C, 55.90; H, 2.47; N, 10.29. **Found (%)**: C, 55.93; H, 2.51; N, 10.32.

2) 4-Chloro-5-(4-chlorophenyl)-7-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidine; 21b

Brown crystals; yield (83%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3080 (CH aromatic); 1654 (C=N); 1524 (C=C); 1059 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d_6, δ ppm)**: 7.29 (d, 1 H, *J* = 7.8 Hz, pyridyl-C_6-H); 7.59 (s, 1 H, CH-pyrrole); 7.84 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 8.00 - 8.10 (m, 3 H, 4-Cl-C_6H_4-$C_{3,5}$-H & pyridyl-C_5-H); 8.22 (d, 1 H, *J* = 7.8 Hz, pyridyl-C_4-H); 8.52 (s, 1 H, pyridyl-C_2-H); 10.23 (s, 1 H, pyrimidine-C_2-H). **Anal**. **Calc**. (%) for $C_{17}H_{10}Cl_2N_4$ (341.2): C, 59.84; H, 2.95; N, 16.42. **Found (%)**: C, 59.92; H, 2.97; N, 16.51.

3.1.21. General Procedure for Synthesis of Compounds 22a,b

An equimolar mixture of the appropriate 7-(substitutedaryl)-4-chloro-5-(4-chlorophenyl)-7H-pyrrolo[2,3-]pyrimidine **21a,b** (2 mmol.) and morpholine (0.17 g, 0.2 mL, 2 mmol.) was refluxed in absolute ethanol for 9 h (30 mL) in presence of a catalytic amount of TEA (3 - 5 drops). The reaction mixture was allowed to cool then treated with 10% acetic acid. The obtained product was filtered, washed with ethanol then recrystallized from ethanol.

1) 7-(3-Trifluoromethylphenyl)-5-(4-chlorophenyl)-4-morpholino-7H-pyrrolo[2,3-d]pyrimidine; 22a

Yellow cubes; yield (76%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3090 (CH aromatic); 2924, 2862 (CH aliphatic); 1660 (C=N); 1580 (C=C); 1250, 1046 (C-O-C); 1110 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d_6, δ ppm)**: 3.43 (t, 4 H, *J* = 4.5 Hz, morpholine-$C_{2,6}$-H); 3.93 (t, 4 H, *J* = 4.5 Hz, morpholine-$C_{3,5}$-H); 7.33 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.46 - 7.51 (m, 3 H, 3-CF_3-C_6H_4-$C_{5,6}$-H & CH-pyrrole); 7.60 - 7.64 (m, 2 H, 3-CF_3-C_6H_4-$C_{2,4}$-H); 7.79 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.30 (s, 1 H, pyrimidine-C_2-H). **Anal**. **Calc**. **(%)** for $C_{23}H_{18}ClF_3N_4O$ (458.9): C, 60.20; H, 3.95; N, 12.21. **Found (%)**: C, 60.23; H, 3.97; N, 12.28.

2) 7-(Pyridine-3-yl)-5-(4-chlorophenyl)-4-morpholino-7H-pyrrolo[2,3-d]pyrimidine; 22b

Dark brown powder; yield (83%); m.p.: > 300˚C. **IR [KBr, cm^{-1}]**: 3000 (CH aromatic); 2924, 2861 (CH aliphatic); 1620 (C=N); 1550 (C=C); 1270, 1040 (C-O-C); 1110 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 3.40 - 3.43 (m, 4 H, morpholine-$C_{2,6}$-H); 4.13 (t, 4 H, *J* = 4.8 Hz, morpholine-$C_{3,5}$-H); 7.04 (s, 1 H, CH-pyrrole); 7.32 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.54 - 7.70 (m, 3 H, pyridyl-$C_{4,5,6}$-H); 7.81 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H);7.88 (s, 1 H, pyridyl-C_2-H); 8.00 (s, 1 H, pyrimidine-C_2-H). **Anal**. **Calc**. **(%)** for $C_{21}H_{18}ClN_5O$ (391.9): C, 64.37; H, 4.63; N, 17.87. **Found (%)**: C, 64.41; H, 4.67; N, 17.92.

3.1.22. General Procedure for Synthesis of Compounds 23a,b

A mixture of compounds **21a,b** (2 mmol.) and hydrazine hydrate 98% (0.1 g, 0.1 mL, 2 mmol.) was refluxed in absolute ethanol (30 mL) in presence of TEA as a catalyst for 10 h. The reaction mixture was allowed to cool and poured on to crushed ice. The obtained solid was filtered, washed with water and recrystallized from dioxane to yield the target compounds **23a,b**; respectively.

1) 5-(4-Chlorophenyl)-4-hydrazinyl-7-(3-trifluoromethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine; 23a

Faint brown needle crystals; yield (45%); m.p.: > 300˚C. **IR [KBr, cm^{-1}]**: 3400, 3200, 3110 (NH_2, NH); 2923 (CH aromatic); 1590 (C=N); 1573 (C=C); 1031 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 4.06 (s, 2 H, NH_2, D_2O exchangeable); 7.01 (s, 1 H, CH-pyrrole); 7.15 - 7.22 (m, 3 H, 3-CF_3-C_6H_4-$C_{4,5,6}$-H); 7.36 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.67 (d, 2 H, *J*=8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.10 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 9.20 (s, 1 H, pyrimidine-C_2-H); 10.45 (s, 1 H, NH, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{19}H_{13}ClF_3N_5$ (403.8): C, 56.52; H, 3.25; N, 17.34. **Found (%)**: C, 56.54; H, 3.29; N, 17.37.

2) 5-(4-Chlorophenyl)-4-hydrazinyl-7-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidine; 23b

Dark brown powder; yield (56%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3382, 3230, 3120 (NH_2, NH); 2924 (CH aromatic); 1651 (C=N); 1527 (C=C); 1044 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 4.52 (s, 2 H, NH_2, D_2O exchangeable); 7.00 (s, 1 H, CH-pyrrole); 7.32 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.47-7.52 (m, 1 H, pyridyl-C_5-H); 7.56 (d, 1 H, *J* = 6.4 Hz, pyridyl-C_6-H); 7.76 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.83 - 7.86 (m, 2 H, pyridyl $C_{2,4}$-H); 7.88 (s, 1 H, pyrimidine-C_2-H); 8.00 (s, 1 H, NH, D_2O exchangeable). **Anal**. **Calc. (%)** for $C_{17}H_{13}ClN_6$ (336.8): C, 60.63; H, 3.89; N, 24.95. **Found** (%): C, 60.66; H, 3.91; N, 24.97.

3.1.23. General Procedure for Synthesis of Compounds 24a,b

To a stirred solution of the selected ethyl N-1-(substitutedaryl)-4-(4-chlorophenyl)-3-cyano-1H-pyrrol-2-ylformimidate **13a,b** (2 mmol.) in absolute ethanol (50 mL), hydrazine hydrate 98% (0.1 g, 0.1 mL, 2 mmol.) was added and stirring was continued for 5 h at room temperature. The solid product was filtered, washed with ethanol and recrystallized from ethanol/benzene.

1) 3-Amino-5-(4-chlorophenyl)-4-imino-7-(3-trifluoromethylphenyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidines; 24a

Faint yellow powder; yield (42%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3447, 3292, 3183 (NH_2, NH); 2928 (CH aromatic); 1643 (C=N); 1556 (C=C); 1025 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 403 ($M^{+\bullet}$, 1); 85 (100). **Anal**. **Calc**. **(%)** for $C_{19}H_{13}ClF_3N_5$ (403.8): C, 56.52; H, 3.25; N, 17.34. **Found (%)**: C, 56.57; H, 3.31; N, 17.42.

2) 3-Amino-5-(4-chlorophenyl)-4-imino-7-(pyridin-3-yl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidines; 24b

Dark grey powder; yield (57%); m.p.: > 300˚C. **IR [KBr, cm^{-1}]**: 3310, 3192 (NH_2, NH); 2921 (CH aromatic); 1650 (C=N); 1558 (C=C); 1091 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 3.48 (s, 2 H, NH_2, D_2O exchangeable); 6.70 (s, 1 H, CH-pyrrole); 7.24 - 7.31 (m, 2 H, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.42 - 7.51 (m, 3 H, pyridyl-$C_{4,5,6}$-H); 7.82 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.28 (s, 1 H, pyridyl-C_2-H); 9.40 (s, 1 H, pyrimidine-C_2-H); 10.60 (s, 1 H, imino NH, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{17}H_{13}ClN_6$ (336.8): C, 60.63; H, 3.89; N, 24.95. **Found (%)**: C, 60.68; H, 3.92; N, 24.97.

3.1.24. General Procedure for Synthesis of Compounds 25a,b

An equimolar mixture of the selected 7-(substitutedaryl)-5-(4-chlorophenyl)-4-imino-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-3-amine **24a,b** (2 mmol.) and ethyl cyanoacetate (0.23 g, 0.1 mL, 2 mmol.) was refluxed in absolute ethanol (30 mL) containing few drops of glacial acetic acid (3 - 5 drops) for 18 h. The reaction mixture was concentrated, then left to cool and the solid product was filtered, washed with ethanol then recrystallized from ethanol.

1) 2-[9-(4-Chlorophenyl)-7-(3-trifluoromethylphenyl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl]-acetonetrile; 25a

Faint brown powder; yield (47%); m.p.: 280˚C - 282˚C. **IR [KBr, cm^{-1}]**: 2934 (CH aromatic); 2850 (CH aliphatic); 2263 (C≡N); 1632 (C=N); 1569 (C=C); 1091 (*p*-Cl-phenyl); **MS** m/z (relative intensity %):454 ($M^{+\bullet}$+2, 0.3); 452 ($M^{+\bullet}$, 1); 58 (100). **Anal**. **Calc**. **(%)** for $C_{22}H_{12}ClF_3N_6$ (452.8): C, 58.35; H, 2.67; N, 18.56. **Found (%)**: C, 58.41; H, 2.69; N, 18.62.

2) 2-[9-(4-Chlorophenyl)-7-(pyridin-3-yl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl]acetonitrile; 25b

Dark brown powder; yield (57%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3000 (CH aromatic); 2924, 2868 (CH aliphatic); 2200 (C≡N); 1641 (C=N); 1533 (C=C); 1026 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 4.16 (s, 2 H, CH_2); 7.10 (s, 1 H, CH-pyrrole); 7.32 - 7.34 (m, 2 H, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.42 - 7.62 (m, 3 H, pyridyl-$C_{4,5,6}$-H); 7.87 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.09 (s, 1 H, pyridyl-C_2-H); 9.70 (s, 1 H, pyrimidine-C_2-H). **Anal**. **Calc**. **(%)** for $C_{20}H_{12}ClN_7$ (385.8): C, 62.26; H, 3.14; N, 25.41. **Found (%)**: C, 62.32; H, 3.18; N, 25.47.

3.1.25. General Procedure for Synthesis of Compounds 26a,b

An equimolar mixture of the appropriate 7-(substitutedaryl)-3-amino-5-(4-chlorophenyl)-4-imino-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidines **24a,b** (2 mmol.), carbon disulfide (0.15 g, 2 mmol.) and KOH (0.11 g, 2 mmol.) was refluxed for 9 h in absolute ethanol (30 mL). The reaction mixture was allowed to cool then poured on to crushed ice and neutralized with few drops of c.HCl. The obtained solid product was filtered off, washed thoroughly with water then recrystallized from dioxane.

1) 9-(4-Chlorophenyl)-7-(3-trifluoromethylphenyl)-3,7-dihydro-2H-pyrrolo[3,2-e][1,2,4]triazolo[1,5- c]pyrimidin-2-thione; 26a

Yellow crystals; yield (57%); m.p.: 274˚C - 276˚C. **IR [KBr, cm^{-1}]**: 3230, 3140 (NH); 2922 (CH aromatic); 1650 (C=N); 1522 (C=C); 1464, 1320, 1170, 1002 (I, II, III, IV bands N-C=S); 1108 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 447 ($M^{+\bullet}$+2, 6); 446 ($M^{+\bullet}$+1, 7); 56 (100). **Anal**. **Calc**. **(%)** for $C_{20}H_{11}ClF_3N_5S$ (445.8): C, 53.88; H, 2.49; N, 15.71. **Found (%)**: C, 53.91; H, 2.52; N, 15.76.

2) 9-(4-Chlorophenyl)-7-(pyridin-3-yl)-3,7-dihydro-2H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-2-thione; 26b

Brown needle crystals**;** yield (75%); m.p.: 310˚C - 312˚C. **IR [KBr, cm^{-1}]**: 3275, 3125 (NH); 3005 (CH aromatic); 1605 (C=N); 1542 (C=C); 1460, 1398, 1260, 1108 (I, II, III, IV bands N-C=S); 1020 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 3.40 (s, 1 H, NH, D_2O exchangeable); 7.00 (s, 1 H, CH-pyrrole); 7.34 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.48 - 7.51 (m, 1 H, pyridyl-C_5-H); 7.58 (d, 1 H, *J* = 6.4 Hz, pyridyl-C_6-H); 7.79 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.86 (d, 1 H, *J* = 6.4 Hz, pyridyl-C_4-H); 8.30 (s, 1 H, pyridyl-C_2-H); 8.47 (s, 1 H, pyrimidine-C_2-H). **Anal**. **Calc**. **(%)** for $C_{18}H_{11}ClN_6S$ (378.8): C, 57.07; H, 2.93; N, 22.18. **Found (%)**: C, 57.12; H, 2.96; N, 22.21.

3.1.26. General Procedure for Synthesis of Compounds 27a,b

The appropriate 7-(substitutedaryl)-3-amino-5-(4-chlorophenyl)-4-imino-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine **24a,b** (2 mmol.) was refluxed in excess triethyl orthoformate (10 mL) for 12 h. The reaction mixture was left to cool and the solid product was filtered, washed with ethanol then recrystallized from glacial acetic acid.

1) 9-(4-Chlorophenyl)-7-(3-trifluoromethylphenyl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine; 27a

Faint yellow crystals; yield (47%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3000 (CH aromatic); 1620 (C=N); 1561 (C=C); 1025 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 6.40 (s, 1 H, CH-pyrrole); 6.80 - 6.85 (m, 3 H, 3-CF_3-C_6H_4-$C_{4,5,6}$-H); 6.92 - 6.97 (m, 2 H, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.28 - 7.35 (m, 2 H, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.45 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 7.48 (s, 1 H, triazole-C_3-H); 8.58 (s, 1 H, pyrimidine-C_2-H). **Anal**. **Calc**. **(%) for** $C_{20}H_{11}ClF_3N_5$ (413.8): C, 58.05; H, 2.68; N, 16.93. **Found (%)**: C, 58.10; H, 2.71; N, 16.96.

2) 9-(4-Chlorophenyl)-7-(pyridin-3-yl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine; 27b

Dark brown powder, yield (56%); m.p.: 278˚C - 280˚C. **IR [KBr, cm^{-1}]**: 2924 (CH aromatic); 1647 (C=N); 1562 (C=C); 1027 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm):** 6.92 - 6.97 (m, 1 H, pyridyl-C_5-H); 7.26 (s, 1 H, CH-pyrrole); 7.30 (d, 1 H, *J* = 7.8 Hz, pyridyl-C_6-H); 7.46 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.78 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.18 - 8.22 (m, 1 H, pyridyl-C_4-H); 8.50 (s, 1 H, pyridyl-C_2-H); 8.63 (s, 1 H, triazole-C_3-H); 9.00 (s, 1 H, pyrimidine-C_2-H). **Anal**. **Calc**. **(%)** for $C_{18}H_{11}ClN_6$ (346.8): C, 62.34; H, 3.20; N, 24.23. **Found (%)**: C, 62.38; H, 3.27; N, 24.28.

3.1.27. General Procedure for Synthesis of Compounds 28a,b

An equimolar mixture of the selected compound **24a,b** (2 mmol.) and phenyl isothiocyanate (0.27 g, 0.24 mL, 2 mmol.) was refluxed for 7 h in absolute ethanol (30 mL) containing few drops TEA (2 - 4 drops). The reaction mixture was left to cool and the obtained product was filtered off, washed with ethanol then recrystallized from ethanol.

1) 2-Amino-9-(4-chlorophenyl)-N-phenyl-7-(3-trifluoromethylphenyl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c] pyrimidine; 28a

Pale yellowish needle crystals; yield (42%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3220 (NH); 2924 (CH aromatic); 1627 (C=N); 1554 (C=C); 1091 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 7.00 (s, 1 H, CH-pyrrole); 7.12 - 7.15 (m, 3 H, C_6H_5-$C_{3,4,5}$-H); 7.32 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.36-7.40 (m, 3 H, 3-CF_3-C_6H_4-$C_{4,5,6}$-H); 7.47 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.80 (d, 2 H, *J* = 7.2 Hz, C_6H_5-$C_{2,6}$-H); 7.83 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 9.70 (s, 1 H, pyrimidine-C_2-H); 10.40 (s,1 H, NH, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{26}H_{16}ClF_3N_6$ (504.9): C, 61.85; H, 3.19; N, 16.65. **Found (%)**: C, 61.88; H, 3.23; N, 16.71.

2) 2-Amino-9-(4-chlorophenyl)-N-phenyl-7-(pyridin-3-yl)-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine; 28b

Grey crystals; yield (56%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3189 (NH); 3002, 2924 (CH aromatic); 1610 (C=N); 1550 (C=C); 1087 (*p*-Cl phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 6.93 (t, 1 H, *J* = 7.5 Hz, C_6H_5-C_4-H); 7.27 (s, 1 H, CH-pyrrole); 7.31 (d, 2 H, *J* = 7.5 Hz, C_6H_5-$C_{3,5}$-H); 7.38 - 7.48 (m, 2 H, pyridyl-$C_{5,6}$-H); 7.55 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.65 (d, 2 H, *J* = 7.5 Hz, C_6H_5-$C_{2,6}$-H); 7.87 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.22 - 8.32 (m, 1 H, pyridyl-C_4-H); 8.67 (s, 1 H, pyridyl-C_2-H); 9.87 (s, 1 H, pyrimidine-C_2-H); 10.20 (s, 1 H, NH, D_2O exchangeable). **^{13}C (DMSO-d$_6$)**: 107.9 (pyrrolotriazolopyrimidine-C_{9a}); 116.5 (pyrrolo-triazolopyrimidine-C_8); 116.8 (N-C_6H_5-$C_{2,6}$); 120.9 (N-C_6H_5-C_4); 123.6 (4-Cl-C_6H_4-C_1); 124 (pyridyl-C_5); 126 (pyrrolotriazolopyrimidine-C_9); 128 (pyridyl-C_6); 128.9 (4-Cl-C_6H_4-$C_{2,6}$); 129.7 (4-Cl-C_6H_4-$C_{3,5}$); 129.9 (N-C_6H_5-$C_{3,5}$); 131.5 (4-Cl-C_6H_4-C_6); 133.9 (pyridyl-C_1); 136 (N-C_6H_5-C_1); 139.4 (pyrrolotriazolopyrimidine-C_5); 141.2 (pyridyl-C_2); 144.6 (pyridyl-C_4); 146 (pyrrolotriazolopyrimidine-C_{9b}); 155.6 (pyrrolotriazolopyrimidine-C_{6a}); 157.9 (pyrrolotriazolopyrimidine-C_2). **Anal**. **Calc**. **(%)** for $C_{24}H_{16}ClN_7$ (437.9): C, 65.83; H, 3.68; N, 22.39. **Found (%)**: C, 65.87; H, 3.72; N, 22.43.

3.1.28. General Procedure for Synthesis of Compounds 29a,b

A mixture of the appropriate 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and sodium azide (0.13 g, 2 mmol.) and ammonium chloride (0.22 g, 2 mmol.) was heated in water bath for 10 h. in excess DMF (15 mL). The reaction mixture was allowed to cool, then triturated with water. The solid product was filtered off, washed with ethanol then recrystallized from glacial acetic acid.

1) 2-Amino-4-(4-chlorophenyl)-1-(3-trifluoromethylphenyl)-3-(1H-tetrazol-5-yl)-1H-pyrrole; 29a

Pale orange crystals; yield (73%); m.p.: >300˚C **IR [KBr, cm^{-1}]**: 3280, 3180 (NH_2, NH); 2923 (CH aromatic); 1559 (C=C); 1383 (N=N); 1081 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 405 ($M^{+\bullet}$+1, 1); 58 (100). **Anal**. **Calc**. **(%)** for $C_{18}H_{12}ClF_3N_6$ (404.8): C, 53.41; H, 2.99; N, 20.76. **Found (%)**: C, 53.48; H, 2.97; N, 20.88.

2) 2-Amino-4-(4-chlorophenyl)-1-(pyridin-3-yl)-3-(1H-tetrazol-5-yl)-1H-pyrrole; 29b

Dark brown needle crystals; yield (92%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3345, 3200 (NH_2, NH); 2926 (CH aromatic); 1520 (C=C); 1419 (N=N); 1096 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 5.20 (s, 2 H, NH_2, D_2O exchangeable); 6.80 (s, 1 H, CH-pyrrole); 7.23 - 7.28 (m, 1 H, pyridyl-C_5-H); 7.45 (d, 1 H, *J* = 6.5 Hz, pyridyl-C_6-H); 7.53 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.61 (d, 1 H, *J* = 6.5 Hz, pyridyl-C_4-H); 7.92 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.20 (s, 1 H, pyridyl-C_2-H); 9.92 (s, 1 H, NH, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{16}H_{12}ClN_7$ (337.8): C, 56.89; H, 3.58; N, 29.03. **Found (%)**: C, 56.91; H, 3.54; N, 29.08.

3.1.29. General Procedure for Synthesis of Compounds 30a,b

A mixture of the appropriate 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.), CS_2 (0.15 g, 0.13 mL, 2 mmol.) and excess ethylene diamine (5 mL) was refluxed in a water bath for 7 h. The reaction mixture was allowed to cool then triturated with ethanol. The obtained product was filtered off, washed with ethanol then recrystallized from dioxane.

1) 2-Amino-4-(4-chlorophenyl)-3-(4,5-dihydro-1H-imidazol-2-yl)-1-(3-trifluoromethylphenyl)-1H-pyrrole; 30a

Yellow powder; yield (67%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3250, 3120 (NH_2, NH); 3000 (CH aromatic); 2950, 2850 (CH aliphatic); 1514 (C=C); 1100 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 406 ($M^{+\bullet}$+2, 0.1);

405 ($M^{+\bullet}$+1, 0.1); 404 ($M^{+\bullet}$, 0.1); 56 (100). **Anal**. **Calc. (%)** for $C_{20}H_{16}ClF_3N_4$ (404.8): C, 59.34; H, 3.98; N, 13.84. **Found (%)**: C, 59.39; H, 3.92; N, 13.87.

2) 2-Amino-4-(4-chlorophenyl)-3-(4,5-dihydro-1H-imidazol-2-yl)-1-(pyridin-3-yl)-1H-pyrrole; 30b

Grey crystals;yield (83%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3360; 3145 (NH_2, NH); 3050 (CH aromatic); 2890 (CH aliphatic); 1654 (C=N); 1520 (C=C); 1090 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 4.75 (s, 1 H, NH, D_2O exchangeable); 5.64 - 5.67 (m, 4 H, imidazolidine-$C_{4,5}$-H); 7.37 (s, 1 H, CH-pyrrole); 7.40 (s, 2 H, NH_2, D_2O exchangeable); 7.51 - 7.54 (m, 2 H, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.57 - 7.62 (m, 1 H, pyridyl-C_5-H); 7.65 - 7.66 (m, 1 H, pyridyl-C_6-H); 8.01 - 8.03 (m, 2 H, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.04 - 8.05 (m, 1 H, pyridyl-C_4-H); 8.06 (s, 1 H, pyridyl-C_2-H). **Anal**. **Calc**. **(%)** for $C_{18}H_{16}ClN_5$ (337.8): C, 64.00; H, 4.77; N, 20.73. **Found (%)**: C, 64.16; H, 4.81; N, 20.79.

3.1.30. General Procedure for Synthesis of Compounds 31a,b

A mixture of the appropriate 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) and CS_2 (0.13 mL, 0.15 g, 2 mmol.) was heated in excess pyridine (10 mL) in a water bath for 10 h, then left to cool. The solid product collected, washed with ethanol then recrystallized from ethanol.

1) 5-(4-Chlorophenyl)-7-(3-trifluoromethylphenyl)-1H-pyrrolo[2,3-d]pyrimidin-2,4(3H,7H)-dithione; 31a

Faint yellow needle crystals;yield (62%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3236 (NH); 3050 (CH aromatic); 1622 (C=N); 1560 (C=C); 1424, 1328, 1129, 1005 (I, II, III, IV bands N-C=S); 1129 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 8.10 (s, 1 H, pyrimidine-N_3-H, D_2O exchangeable); 7.35 - 7.41 (m, 1H, 3-CF_3-C_6H_4-C_5-H); 7.50 (s, 1H, CH-pyrrole); 7.56 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.61 - 7.63 (m, 1 H, 3-CF_3-C_6H_4-C_6-H); 7.78 - 7.82 (m, 1 H, 3-CF_3-C_6H_4-C_4-H); 7.93 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.58 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 8.76 (s, 1 H, pyrimidine-N_1-H, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{19}H_{11}ClF_3N_3S_2$ (437.9): C, 52.11; H, 2.53; N, 9.60. **Found (%)**: C, 52.17; H, 2.63; N, 9.71.

2) 5-(4-Chlorophenyl)-7-(pyridin-3-yl)-1H-pyrrolo[2,3-d]pyrimidin-2,4(3H,7H)-dithione; 31b

Brown needle crystals; yield (78%); m.p.: > 300˚C. **IR [KBr, cm^{-1}]**: 3306, 3207 (NH); 2923 (CH aromatic); 1641 (C=N); 1534 (C=C); 1480, 1390, 1128, 1000 (I, II, III, IV bands N-C=S); 1128 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 372 ($M^{+\bullet}$+2, 1); 371 ($M^{+\bullet}$+1, 1); 58 (100). **Anal**. **Calc**. **(%)** for $C_{17}H_{11}ClN_4S_2$ (370.9): C, 55.05; H, 2.99; N, 15.11. **Found (%)**: C, 55.01; H, 2.86; N, 15.16.

3.1.31. General Procedure for Synthesis of Compounds 32a,b

The selected 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile **4a,b** (2 mmol.) was dissolved in a mixture of glacial acetic acid/c.HCl (10:7) (20 mL). To such solution, a solution of sodium nitrite (0.14 g, 2 mmol.) in (1 mL) water was added drop wise while stirring at 0˚C - 5˚C then stirring was continued for 3 h while maintaining the reaction temperature at 5˚C. The solid product was then collected, washed with ethanol then recrystallized from glacial acetic acid.

1) 5-(4-Chlorophenyl)-7-(3-trifluoromethylphenyl)-3H-pyrrolo[2,3-d][1,2,3]triazine-4(7H)one; 32a

Yellow powder; yield (62%); m.p.:287˚C - 289˚C. **IR [KBr, cm^{-1}]**: 3100 (NH); 3050 (CH aromatic); 1691 (C=O); 1528 (C=C); 1411 (N=N); 1112 (*p*-Cl-phenyl).**^{1}H NMR (DMSO-d$_6$, δ ppm)**: 7.25 (s, 1 H, CH-pyrrole); 7.41 (s, 1 H, NH, D_2O exchangeable); 7.54 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.62 - 7.86 (m, 4 H, 3-CF_3-C_6H_4-$C_{2,4,5,6}$-H); 7.92 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H). **Anal**. **Calc**. **(%)** for $C_{18}H_{10}ClF_3N_4O$ (390.7): C, 55.33; H, 2.58; N, 14.34. **Found** (%): C, 55.33; H, 2.58; N, 14.34.

2) 5-(4-Chlorophenyl)-7-(pyridin-3-yl)-3H-pyrrolo[2,3-d][1,2,3]triazin-4(7H)-one; 32b

Dark grey crystals; yield (78%); m.p.: 267˚C - 269˚C. **IR [KBr, cm^{-1}]**: 3114 (NH); 3010 (CH aromatic); 1690 (C=O); 1531 (C=C); 1407 (N=N); 1088 (*p*-Cl-phenyl). **^{1}H NMR(DMSO-d$_6$, δ ppm)**: 7.28 (s, 1 H, CH-pyrrole); 7.45 (s, 1 H, NH, D_2O exchangeable); 7.52 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.55 - 7.62 (m, 4 H, pyridyl-$C_{2,4,5,6}$-H); 7.91 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H). **Anal**. **Calc**. **(%)** for $C_{16}H_{10}ClN_5O$ (323.7): C, 59.36; H, 3.11; N, 21.63. **Found (%)**: C, 59.36; H, 3.11; N, 21.63.

3.1.32. General Procedure for Synthesis of Compounds 33a,b

To a stirred solution of the selected ethyl 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrol-3-carboxylate **4c, d** (2 mmol.) in absolute ethanol (50 mL), hydrazine hydrate 98% (0.1 g, 0.12 mL, 2 mmol.) was added and the reaction was refluxed for 6 h. The solid product was isolated by filtration, washed with ethanol and recrystallized from ethanol.

1) 2-Amino-4-(4-chlorophenyl)-1-(3-trifluoromethylphenyl)-1H-pyrrol-3-carbohydrazide; 33a

Pale yellow crystals; yield (67%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3450, 3401, 3200 (NH_2, NH); 2934 (CH aromatic); 1690 (C=O); 1520 (C=C); 1021 (*p*-Cl-phenyl).**^{1}H NMR (DMSO-d$_6$, δ ppm)**: 5.30 (s, 2 H, NH-NH_2, D_2O exchangeable); 6.74 (s, 1 H, CH-pyrrole); 7.31 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.38 - 7.45 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.50 - 7.60 (m, 2 H, 3-CF_3-C_6H_4-$C_{4,6}$-H); 7.87 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H), 8.35 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 8.50 (s, 2 H, pyrrole-C_2-NH_2, D_2O exchangeable); 8.59 (s, 1 H, NH, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{18}H_{14}ClF_3N_4O$ (394.8): C, 54.76; H, 3.57; N, 14.19. **Found (%)**: C, 54.65; H, 3.43; N, 14.23.

2) 2-Amino-4-(4-chlorophenyl)-1-(pyridin-3-yl)-1H-pyrrole-3-carbohydrazide; 33b

Faint brown crystals; yield (72%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3390, 3213 (NH_2, NH); 2980 (CH aromatic); 1680 (C=O), 1522 (C=C); 1031 (*p*-Cl-phenyl); **MS** m/z (relative intensity %): 329 ($M^{+\bullet}$+2, 1); 327 ($M^{+\bullet}$, 9); 140 (100). **Anal**. **Calc**. **(%)** for $C_{16}H_{14}ClN_5O$ (327.8): C, 58.63; H, 4.31; N, 21.37. **Found (%)**: C, 58.71; H, 4.42; N, 21.43.

3.1.33. General Procedure for Synthesis of Compounds 34a,b

The selected ethyl 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrol-3-carboxylate **4c, d** (2 mmol.) was refluxed for 7 h in excess acetic anhydride (30 mL). The reaction mixture was concentrated under reduced pressure and the residue was collected by filtration, washed with ethanol and recrystallized from ethanol.

1) Ethyl 2-acetamido-4-(4-chlorophenyl)-1-(3-trifluoromethylphenyl)-1H-pyrrol-3-carboxylate; 34a

Faint orange powder; yield (59%); m.p.: > 300˚C. **IR [KBr, cm^{-1}]**: 3293, 3180 (NH); 2927 (CH aromatic); 2860 (CH-aliphatic); 1689, 1650 (C=O); 1421 (C=C); 1250, 1026 (C-O-C); 1120 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 1.17 - 1.23 (m, 3 H, CH_2CH_3); 2.05 (s, 3 H, $COCH_3$); 3.91 - 4.01 (m, 2 H, CH_2CH_3); 7.30 (d, 1 H, *J* = 7.8 Hz, 3-CF_3-C_6H_4-C_6-H); 7.37 (d, 1 H, *J* = 7.8 Hz, 3-CF_3-C_6H_4-C_4-H); 7.50 - 7.55 (m, 3 H, 4-Cl-C_6H_4-$C_{2,6}$-H & 3-CF_3-C_6H_4-C_5-H); 7.75 (s, 1 H, CH-pyrrole); 7.84 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.08 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 10.45 (s, 1 H, NH, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{22}H_{18}ClF_3N_2O_3$ (450.8): C, 58.61; H, 4.02; N, 6.21. **Found (%)**: C, 58.64; H, 4.10; N, 6.28.

2) Ethyl 2-acetamido-4-(4-chlorophenyl)-1-(pyridin-3-yl)-1H-pyrrole-3-carboxylate; 34b

Dark brown needle crystals; yield (71%); m.p.: > 300˚C. **IR [KBr, cm^{-1}]**: 3220 (NH); 3096 (CH aromatic); 2921, 2858 (CH-aliphatic); 1693 (C=O); 1544 (C=C); 1245, 1024 (C-O-C); 1110 (*p*-Cl-phenyl). **MS** m/z (relative intensity %): 385 ($M^{+\bullet}$+2, 0.6); 384 ($M^{+\bullet}$+1, 0.2); 383 ($M^{+\bullet}$, 0.2); 58 (100). **Anal**. **Calc**. **(%)** for $C_{20}H_{18}ClN_3O_3$ (383.8): C, 62.58; H, 4.73; N, 10.95. **Found (%)**: C, 62.55; H, 4.81; N, 10.97.

3.1.34. General Procedure for Synthesis of Compounds 35a,b

An equimolar mixture of the selected 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carbohydrazide **33a,b** (2 mmol.) and glucose (0.22 g, 2 mmol.) was refluxed in absolute ethanol (30 mL) for 12 h, then left to cool. The obtained product was filtered off, washed with ethanol then recrystallized from ethanol.

1) 2-Amino-4-(4-chlorophenyl)-N'-2,3,4,5,6-pentahydroxy-1-hexylidene)-1-(3-trifluoromethylphenyl)-1H-pyr-rol-3-carbohydrazide; 35a

Yellow needle crystals; yield (89%); m.p.: 296˚C - 298˚C. **IR [KBr, cm^{-1}]**: multiple absorption bands at 3496, 3438 (OH); 3360, 3310, 3250 (NH_2, NH); 3000 (CH aromatic); 2924, 2860 (CH-aliphatic); 1710 (C=O); 1644 (C=N); 1542 (C=C); 1036 (*p*-Cl-phenyl). **MS** m/z (relative intensity %): 558 ($M^{+\bullet}$+2, 0.1); 57 (100). **Anal**. **Calc**. **(%)** for $C_{24}H_{24}ClF_3N_4O_6$ (556.9): C, 51.76; H, 4.34; N, 10.06. **Found (%)**: C, 51.81; H, 4.31; N, 10.15.

2) 2-Amino-4-(4-chlorophenyl)-N'-2,3,4,5,6-pentahydroxy-1-hexylidene)-1-(pyridin-3-yl)-1H-pyrrol-3-car-bohydrazide; 35b

Buff needle crystals; yield (91%); m.p.: 326˚C - 328˚C. **IR [KBr, cm^{-1}]**: 3400, 3386 (OH); 3300, 3210(NH_2, NH); 3000 (CH aromatic); 2920 (CH-aliphatic); 1700 (C=O), 1640 (C=N); 1470 (C=C); 1090 (*p*-Cl-phenyl). **MS** m/z (relative intensity %): 490 ($M^{+\bullet}$+1, 0.2); 57 (100). **Anal**. **Calc**. **(%)** for $C_{22}H_{24}ClN_5O_6$ (489.9): C, 53.94; H, 4.94; N, 14.30. **Found (%)**: C, 53.97; H, 4.91; N, 14.38.

3.1.35. General Procedure for Synthesis of Compounds 36a,b

The selected ethyl 1-(substitutedaryl)-2-acetamido-4-(4-chlorophenyl)-1H-pyrrol-3-carboxylates **34a,b** (2 mmol.) was refluxed with hydrazine hydrate 98% (0.1 g, 0.12 mL, 2 mmol.) in absolute ethanol (30 mL) for 6 h. The reaction mixture was allowed to cool and the solid product was filtered, washed with ethanol then recrystallized

from dioxane.

1) 3-Amino-5-(4-chlorophenyl)-2-methyl-7-(3-trifluoromethylphenyl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one; 36a

Pale orange crystals; yield (71%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3280, 3200 (NH_2); 2924 (CH aromatic); 2861 (CH-aliphatic); 1680 (C=O); 1428 (C=C); 1105 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 2.07 (s, 3 H, CH_3); 4.91 (s, 2 H, NH_2, D_2O exchangeable); 7.30 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.33 (s, 1 H, CH-pyrrole); 7.38 - 7.48 (m, 2 H, 3-CF_3-C_6H_4-$C_{5,6}$-H); 7.50 - 7.60 (m, 1 H,3-CF_3-C_6H_4-C_4-H); 7.85 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.09 (s, 1 H, 3-CF_3-C_6H_4-C_2-H). **Anal**. **Calc**. **(%)** for $C_{20}H_{14}ClF_3N_4O$(418.8): C, 57.36; H, 3.37; N, 13.38. **Found (%)**: C, 57.44; H, 3.31; N, 13.42.

2) 3-Amino-5-(4-chlorophenyl)-2-methyl-7-(pyridin-3-yl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one; 36b

Dark brown crystals; yield (87%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3391, 3185 (NH_2); 2929 (CH aromatic); 2860 (CH-aliphatic); 1690 (C=O), 1543 (C=C); 1033 (*p*-Cl-phenyl). **MS** m/z (relative intensity %): 353 ($M^{+\bullet}$+2, 0.2); 351 ($M^{+\bullet}$, 1); 58 (100). **Anal**. **Calc**. **(%)** for $C_{18}H_{14}ClN_5O$ (351.8): C, 61.46; H, 4.01; N, 19.91. **Found (%)**: C, 61.51; H, 4.07; N, 19.96.

3.1.36. General Procedure for Synthesis of Compounds 37a,b

A solution of the appropriate ethyl 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrol-3-carboxylate **4c, d** (2 mmol.) in (30 mL) ethanolic sodium hydroxide solution [prepared by dissolving sodium hydroxide (0.1 g, 2 mmol.) in (30 mL) absolute ethanol] was heated under reflux for 9 h. The reaction mixture was allowed to cool, then acidified with dilute acetic acid (1.3 mL) and extracted with ether. The obtained product from ethereal solution was collected and recrystallized from ethanol.

1) 2-Amino-4-(4-chlorophenyl)-1-(3-trifluoromethylphenyl)-1H-pyrrol-3-carboxylic acid; 37a

Pale yellow powder; yield (57%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3350 (br. OH); 3119 (NH_2); 2996 (CH aromatic); 1696 (C=O); 1522 (C=C); 1108 (*p*-Cl-phenyl). **MS** m/z (relative intensity %): 382 ($M^{+\bullet}$+2, 1); 380 ($M^{+\bullet}$, 2); 139 (100). **Anal**. **Calc**. **(%)** for $C_{18}H_{12}ClF_3N_2O_2$ (380.7): C, 56.78; H, 3.18; N, 7.36. **Found (%)**: C, 56.82; H, 3.21; N, 7.47.

2) 2-Amino-4-(4-chlorophenyl)-1-(pyridin-3-yl)-1H-pyrrol-3-carboxylic acid; 37b

Grey powder; yield (67%); m.p.: > 300˚C. **IR [KBr, cm^{-1}]**: 3391 (br. OH); 3219 (NH_2); 3050 (CH aromatic); 1684 (C=O); 1517 (C=C); 1089 (*p*-Cl phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 5.37 (s, 2 H, NH_2, D_2O exchangeable); 7.38 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.52 - 7.58 (m, 1 H, pyridyl-C_5-H); 7.59 - 7.68 (m, 1 H, pyridyl-C_6-H); 7.89 (s, 1 H, CH-pyrrole); 7.92 - 7.96 (m, 2 H, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.01 - 8.06 (m, 1 H, pyridyl-C_4-H); 8.07 (s, 1 H, pyridyl-C_2-H); 9.47 (s, 1 H, OH, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{16}H_{12}ClN_3O_2$ (313.7): C, 61.25; H, 3.86; N, 13.39. **Found (%)**: C, 61.27; H, 3.89; N, 13.43.

3.1.37. General Procedure for Synthesis of Compounds 38a,b

An equimolar mixture of the selected ethyl 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrol-3-carboxylate **4c,d** (2 mmol.) and phenyl isothiocyanate (0.27 g, 0.24 mL, 2 mmol.) was refluxed in for 12 h in absolute ethanol (20 mL). The reaction mixture was left to cool and the obtained product was filtered, washed with ethanol then recrystallized from glacial acetic acid.

1) Ethyl 4-(4-chlorophenyl)-2-(3-phenylthioureido)-1-(3-trifluoromethylphenyl)-1H-pyrrol-3-carboxylate; 38a

Faint orange needle crystals; yield (62%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3200 (NH); 2924 (CH aromatic); 2861 (CH-aliphatic); 1720 (C=O); 1560 (C=C); 1457, 1380, 1140, 998 (I, II, III, IV bands N-C=S); 1250, 1031 (C-O-C); 1031 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d$_6$, δ ppm)**: 1.12 - 1.20 (m, 3 H, CH_2CH_3); 4.38 (q, 2 H, *J* = 6 Hz, CH_2CH_3); 6.90 (s, 1 H, CH-pyrrole); 7.10 - 7.17 (m, 3 H, C_6H_5-$C_{3,4,5}$-H); 7.20 - 7.28 (m, 1 H, 3-CF_3-C_6H_4-C_5-H); 7.31 - 7.38 (m, 1 H, 3-CF_3-C_6H_4-C_6-H); 7.51 - 7.58 (m, 3 H, 4-Cl-C_6H_4-$C_{2,6}$-H & 3-CF_3-C_6H_4-C_4-H); 7.70 - 7.78 (m, 2 H, C_6H_5-$C_{2,6}$-H); 7.81 (d, 2 H, *J* = 8.1 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 8.01 (s, 1 H, 3-CF_3-C_6H_4-C_2-H); 11.40 (s, 1 H, pyrrole-C_2-NH, D_2O exchangeable); 11.83 (s, 1 H, C_6H_5-NH, D_2O exchangeable). **Anal**. **Calc**. **(%)** for $C_{27}H_{21}ClF_3N_3O_2S$ (544): C, 59.61; H, 3.89; N, 7.72. **Found (%)**: C, 59.67; H, 3.93; N, 7.81.

2) Ethyl 4-(4-chlorophenyl)-2-(3-phenylthioureido)-1-(pyridin-3-yl)-1H-pyrrole-3-carboxylate; 38b

Dark brown needle crystals; yield (76%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3390, 3213 (NH); 3080 (CH aromatic); 2927, 2820 (CH-aliphatic); 1680 (C=O); 1525 (C=C); 1411, 1360, 1134, 1033 (I, II, III, IV bands N-C=S); 1250, 1090 (C-O-C); 1040 (*p*-Cl-phenyl). **MS** m/z (relative intensity %): 478 ($M^{+\bullet}$+2, 1); 94 (100).

Anal. **Calc**. **(%)** for $C_{25}H_{21}ClN_4O_2S$ (477): C, 62.95; H, 4.44; N, 11.75. **Found (%)**: C, 62.98; H, 4.51; N, 11.78.

3.1.38. General Procedure for Synthesis of Compounds 39a,b

A mixture of the appropriate 1-(substitutedaryl)-2-amino-4-(4-chlorophenyl)-1H-pyrrole-3-carboxylic acid **37a,b** (2 mmol.) and excess acetic anhydride (20 mL) was heated under reflux for 10 h. The reaction was left to cool and the solid product which was formed, was filtered off, washed with ethanol then recrystallized from glacial acetic acid.

1) 5-(4-Chlorophenyl)-2-methyl-7-(3-trifluoromethylphenyl)pyrrolo[2,3-d][1,3]oxazin-4(7H)-one; 39a

Yellow powder; yield (73%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3040 (CH aromatic); 2922, 2852 (CH-aliphatic); 1686 (C=O); 1550 (C=C); 1290, 1088 (C-O-C); 1025 (*p*-Cl-phenyl). **MS** m/z (relative intensity %):404 ($M^{+\bullet}$, 0.2); 57 (100). **Anal**. **Calc**. **(%)** for $C_{20}H_{12}ClF_3N_2O_2$ (404.8): C, 59.35; H, 2.99; N, 6.92. **Found (%)**: C, 59.41; H, 2.95; N, 6.97.

2) 5-(4-Chlorophenyl)-2-methyl-7-(pyridin-3-yl)pyrrolo[2,3-d][1,3]oxazin-4(7H)-one; 39b

Dark brown crystals; yield (83%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3060 (CH aromatic); 2925, 2850 (CH-aliphatic); 1688 (C=O); 1426 (C=C); 1236, 1084 (C-O-C); 1020 (*p*-Cl-phenyl). **MS** m/z (relative intensity %): 338 ($M^{+\bullet}$+1, 0.2); 337 ($M^{+\bullet}$, 0.2); 57 (100). **Anal**. **Calc**. **(%)** for $C_{18}H_{12}ClN_3O_2$ (337.8): C, 64.01; H, 3.58; N, 12.44. **Found (%)**: C, 64.07; H, 3.62; N, 12.51.

3.1.39. General Procedure for Synthesis of Compounds 40a,b

A solution of the selected ethyl 1-(substituted aryl)-4-(4-chlorophenyl)-2-(3-phenylthioureido)-1H-pyrrol-3-carboxylate **38a,b** (2 mmol.) in sodium ethoxide [prepared by dissolving sodium metal (0.1 g, 2 mmol.) in absolute ethanol (30 mL)] was heated under reflux for 8 h. The reaction mixture was acidified with 10% HCl and the obtained product was collected, washed with ethanol and recrystallized from ethanol.

1) 5-(4-Chlorophenyl)-3-phenyl-7-(3-trifluoromethylphenyl)-2-thioxo-2,3-dihydro-1H-pyrrolo[2,3-d]pyrimidin-4(7H)-one; 40a

Faint orange needle crystals; yield (69%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3180 (NH); 2922 (CH aromatic); 1700 (C=O); 1550 (C=C); 1460, 1350, 1134, 1036 (I, II, III, IV bands N-C=S); 1036 (*p*-Cl-phenyl). **^{1}H NMR (DMSO-d_6, δ ppm)**: 5.02 (s,1 H, NH, D_2O exchangeable); 6.60 - 6.78 (m, 5 H, C_6H_5); 7.31 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{2,6}$-H); 7.40 (s, 1 H, CH-pyrrole); 7.48 - 7.61 (m, 2 H, 3-CF_3-C_6H_4-$C_{5,6}$-H); 7.85 (d, 2 H, *J* = 8.4 Hz, 4-Cl-C_6H_4-$C_{3,5}$-H); 7.98 - 8.10 (m, 2 H, 3-CF_3-C_6H_4-$C_{2,4}$-H). **Anal**. **Calc**. **(%)** for $C_{25}H_{15}ClF_3N_3OS$(497.9): C, 60.30; H, 3.04; N, 8.44. **Found (%)**: C, 60.38; H, 3.10; N, 8.48.

2) 5-(4-Chlorophenyl)-3-phenyl-7-(pyridin-3-yl)-2-thioxo-2,3-dihydro-1H-pyrrolo[2,3-d]pyrimidin-4(7H)-one; 40 b

Dark brown needle crystals; yield (69%); m.p.: >300˚C. **IR [KBr, cm^{-1}]**: 3200 (NH); 2924 (CH aromatic); 1690 (C=O); 1541 (C=C); 1455, 1250, 1122, 1037 (I, II, III, IV bands N-C=S); 1037 (*p*-Cl-phenyl). **MS** m/z (relative intensity %): 432 ($M^{+\bullet}$+2, 0.4); 57 (100). **Anal**. **Calc**. **(%)** for $C_{23}H_{15}ClN_4OS$ (430.9): C, 64.11; H, 3.51; N, 13.00. **Found (%)**: C, 64.17; H, 3.61; N, 13.08.

3.2. Biology

3.2.1. Anti-Inflammatory Screening

1) Animals

The screening for anti-inflammatory activity for all the newly synthesized compounds **4a-40b** was carried out by using adult albino rats of both sexes weighing 120 - 150 g which were obtained from animal house laboratory of Nile company, Cairo, Egypt. Rats were divided into eighty four groups; each group consists of five rats per cage in the Department of Pharmacology, Faculty of Medicine, Al-Azhar University.

The rats were kept under constant temperature 30˚C and 12 hours light/dark cycle. All animals were acclimatized in the animal facility for at least two weeks prior the experiments.

The animals were kept fastened for 24 hours prior to the experiment, but they were allowed free access to water [37]. The animal experiments described below comply with the ethical principles and guidelines for the care and use of laboratory animals adopted by the National Egyptian Community.

The equipment used was Dial micrometer model (120 - 1206 Baty, Sussex, England).

2) Anti-inflammatory activity:

Rat paw edema assay was carried out according to Winter *et al*. [38]. Prepared compounds (equimolar to the referencedrug) were dissolved in DMSO and administrated subcutaneously.

One hour after drug administration acute inflammation was induced by injection of 0.05 mL of 1% of carrageenan sodium (Sigma-Aldrich, St. Louis, USA) subcutaneously into the sub planter region of the right hind paw.

The thickness of the injected paw was measured (from dorsal to ventral surfaces) immediately after carrageenan injection and after (1, 2, 3, 4, 5 and 6 hours) by using a micrometer. The size of edema was expressed as the increase in the thickness in mm after carrageenan injection.

The percentage inhibition of edema thickness at each time interval was calculated from the mean effect in control and treated animals according to the equation [39] [40].

$$\%\ \text{Inhibition of edema thickness} = \left[\left(\text{Tc} - \text{Tt}\right)/\text{Tc}\right] \times 100$$

where, Tc and Tt are the mean increase in thickness of the carrageenan injected paw of the control group and drug treated groups; respectively.

Control group: received the excipients (water mixed with few drops of tween 80) followed by carrageenan after 1 hour. Indomethacin (Indocin®) (5 mg/kg) was used as the referencedrug [41]. Then the potencies of compounds were calculated after 6 hours of carrageenan injection where the % edema inhibition reached maximum.

3) Statistical analysis

Results are expressed as (mean ± standard deviation) statistically analyzed using two way analysis of variance (ANOVA) followed by Bonferroni test [42].

3.2.2. Ulcerogenicity

All animals subjected to this experimental test were sacrificed immediately after the last measurement (6 hour), by diethyl ether and stomachs were separated. An opening at the great curvature was made and the stomachs were washed with distilled water and cleaned gently by dipping in normal saline. The mucosal damage was inspected with a 3× magnifying lens for any evidence of hyperemia, hemorrhage or ulcer. For each stomach the mucosal damage was assessed [43].

The percentage ulceration for each group was calculated as follows:

$$\%\ \text{Ulceration} = \frac{\text{Number of animals bearing ulcerin a group}}{\text{Total number of animals in the same group}} \times 100$$

3.2.3. Analgesic Screening

1) Animals:

The screening for analgesic activity for all synthesized compounds **4a-40b** was carried out by using mices of both sexes weighing 25 - 30 g which were obtained from animal house laboratory, Nile company, Cairo, Egypt.

Mices were divided into eighty four groups; each group consists of four mices per cage in the animal facility of Faculty of Medicine, Al-Azhar University. The mices were kept under constant temperature 25˚C and 12 hours light/dark cycle. All animals were acclimatized in the animal facility for at least two weeks prior the experiments.The animals were kept fastened for 24 hours prior to the experiment, but they were allowed free access to water.

2) Assessment of analgesic screening:

The analgesic activity was evaluated according to writhing test reported by Koster *et al.* [44]. The newly synthesized compounds (equimolar to the reference drug) were dissolved in DMSO and administrated to the groups orally (using intragastric tube) followed by injection of 0.6% acetic acid solution (10 mL/kg) after 1 hour [45]. Indomethacin (Indocin®) (2.5 mg/kg) was used as the reference drug.

Stretching movements (arching of the back, developments of the tension in the abdominal muscles, elongation of the body and extension of the forelimbs) were counted as a writhing response. The number of writhes was counted for 15 minutes immediately after the acetic acid injection. The percentage of inhibition of writhes number was calculated as follows:

$$\%\ \text{of Inhibition} = \frac{\text{Nc} - \text{Nt}}{\text{Nc}} \times 100$$

where Nc and Nt are number of writhes in the control group and drug groups; respectively.

3.2.4. Antimicrobial Activity

1) Materials and methods

Antimicrobial activity was examined by the cup-diffusion method [46]. The in-vitro antimicrobialactivity of the synthesized compounds was investigated against several pathogenic representatives; Gram-negative bacteria; *Pseudomonas aeruginosa* (ATCC 27853) and *Escherichia coli* (ATCC 8739) and Gram-positive bacteria; *Staphylococcus aureus* (ATCC 25923) and *Candida albicans* (ATCC 10231) as a representative for fungi. All microorganisms used were obtained from the culture collection of the Department of Microbiology and Immunology, Faculty of Pharmacy (boys), Al-Azhar University, Cairo, Egypt.

Media for disc sensitivity tests were the nutrient agar and Muller-Hinton agar (MHA) purchased from Difco (USA). Non-sterile powder of the tested compounds was dissolved in dimethylformamide in a concentration of 1 mg/mL. Each 100 mL of sterile molten agar (at 45˚C) received 1 mL of 6 h cultured broth with the microorganism, then the seeded agar was poured into sterile petri dishes. Cups (8 mm in diameter) were cut in the agar. Each cup received 0.1 mL of the 1 mg/mL solution of the test compounds. Plates were then incubated at 37˚C for 24 h. for bacteria and 48 h. for fungi. Ampicillin (Bioanalyses Turkey) and Fluconazole (Sigma-Aldrich, USA) were used as reference substances.

3.3. Computer Aided Docking

3.3.1. Materials

All the molecular studies were carried out on an Intel Pentium 1.6 GHz processor, 512 MB memory with windows XP operating system using Molecular Operating Environment (MOE 10.2008) software provided by chemical computing group, Montreal, Canada.

All the minimizations were performed with MOE until a RMSD gradient of 0.05 $Kcal \cdot mol^{-1} \cdot A^{0-1}$ with MMFF94X force field and the partial charges were automatically calculated.

3.3.2. General Methodology

The coordinates of the X-ray crystallographic structure of the COX-2 complex with its co-crystallized ligand (Diclofenac) in the file (PDP ID: 1CX2) was obtained from the protein data bank (PDB). Enzyme structures were checked for missing atoms, bonds and contacts. The ligand molecules were constructed using the builder molecule and were energy minimized. The enzyme was prepared for docking studies where Ligand molecule was removed from the enzyme active site. Also, hydrogen atoms were added to the structure with their standard geometry. However, MOE Alpha site Finder was used for the active sites search in the enzyme structure and dummy atoms were created from the obtained alpha spheres.

4. Conclusions

It can be concluded that, among the newly synthesized compounds, compounds **5d, 9d, 11b, 12a, 13b** and **32a** showed multiple activities; anti-inflammatory, analgesic and anti-bacterial activities. Furthermore, it is to be noted that, some functions exerted multiple activities among these functions are 2,4-dichlorobenzylidine imino function in 2-position of pyrrole as in compound **5d**. Also, the thiourea and phenylurea function as in compounds **9d** and **11b**, respectively. In addition to, imino function such as iminopyrrolopyrimidine thione and ethoxymethyleneimino functions as in compounds **12a** and **13b**, respectively, besides to, the pyrrolo[1,2,3]triazine derivative **32a**.

In addition to, the molecular docking for the twenty most active anti-inflammatory compounds was performed on the active site of COX-2 enzyme in a trial to predict their mode of action as anti-inflammatory drugs, in which the compounds showed several interactions leading to the conclusion that they might exert their action through inhibition of COX-2 enzyme.

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Department, Faculty of Pharmacy (Girls), Al-Azhar University. The Molecular docking study was performed in the pharmaceutical Chemistry Department, Faculty of Pharmacy, Alexandria University.

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