SYNTHESIS OF NEW PYRROLE AND PYRROLO[2,3-*d*]PYRIMIDINE DERIVATIVES OF POTENTIAL ANTIOXIDANT ACTIVITY

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New 2-amino-3-cyanopyrrole derivatives were prepared and converted to 7-deazapurines. 7-Deazaadenine **6** was synthesized by different methods and alkylated with alkyl iodides to afford the quaternized 3-alkylpyrrolopyrimidinium iodide salts **8**. The latter salts were dequaternized to *N*-alkylpyrrolo[2,3-*d*]pyrimidin-4-amines **12**. Compounds **12** were identical to the products obtained from reactions of 4-chloro-7-(4-fluorophenyl)-5-*p*-tolyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine **11** with methyl- or ethylamine in the presence of a catalyst. The thione **13** and its related 4-methylthio- and 4-ylcarbonothioate derivatives **14a**, **14b** were obtained. The triazolo- **17a–17e**, benzenesulfonamido- **19**, and tetrazolopyrrolopyrimidine **21** derivatives were synthesized. Several examples of the synthesized pyrrole- and pyrrolo[2,3-*d*]pyrimidine derivatives showed high to remarkable antioxidant scavenging activity as measured by their ability to scavenge the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical

Keywords: Antioxidant activity; Pyrrole; Pyrrolo[2,3-*d*]pyrimidine; Quaternization; Triazole; Tetrazole.

It is well known that pyrrolic compounds such as polypyrroles, poly- or heteroarylpyrroles present an electronic delocalization, conferring to these molecules electric conductor and oxidizable properties[1], also, other 2-aminopyrrole-3-carbonitrile derivatives having β-enaminonitrile moiety are well known to be highly reactive and were used as intermediates for the synthesis of new pyrrolo[2,3-*d*]pyrimidine derivatives[2]. 7-Deazapurine (pyrrolo[2,3-*d*]pyrimidine) is a heterobicyclic system bearing structural analogy both to purine and indole and as such might be expected to have pharmacological interest and perhaps clinical value. This heterosystem is widely distributed in nature, being the part of antibiotics: tubercidin, toyocamycin, sangivamycin, cadeguomycin, rigidin alkaloids[3]. Moreover, some 2,4-diaminopyrrolo[2,3-*d*]pyrimidine derivatives were identified to have a much greater blood brain barrier (BBB) penetration capacity and

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high-lipophilic antioxidant activity with protective effects[4]. For example, some 2,4-diaminopyrrolo[2,3-*d*]pyrimidines and 6,7-dimethyl-2,4-dipyrrolidin-1-yl-7*H*-pyrrolo[2,3-*d*]pyrimidine were reported for their antioxidant, neuroprotective, and antiasthma properties[5]. Furthermore, it is well known that organofluorine compounds display a variety of interesting pharmacological and agrochemical properties. A series of fluoro-substituted 4-(dialkylamino)pyrrolo[2,3-*d*]pyrimidines has been synthesized and reported for their binding affinity for corticotrophin releasing hormone type 1 receptor ($CRHR_1$) and some other compounds were presented as promising candidates for the development of ^{18}F-containing non-peptide PET radioligands for $CRHR_1$ [6].

Therefore, it was intended to synthesize new pyrrole- and pyrrolo-[2,3-*d*]pyrimidine derivatives bearing fluorophenyl and *p*-tolyl moieties for their potential antioxidant activity.

RESULTS AND DISCUSSION

2-Amino-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrole-3-carbonitrile (**1**) was prepared under mild Gewald reaction condition[7], from 2-(4-fluorophenylamino)-1-*p*-tolylethanone (prepared from 2-bromo-1-*p*-tolylethanone and *p*-fluoroaniline) upon reaction with malononitrile in the presence of sodium ethoxide.

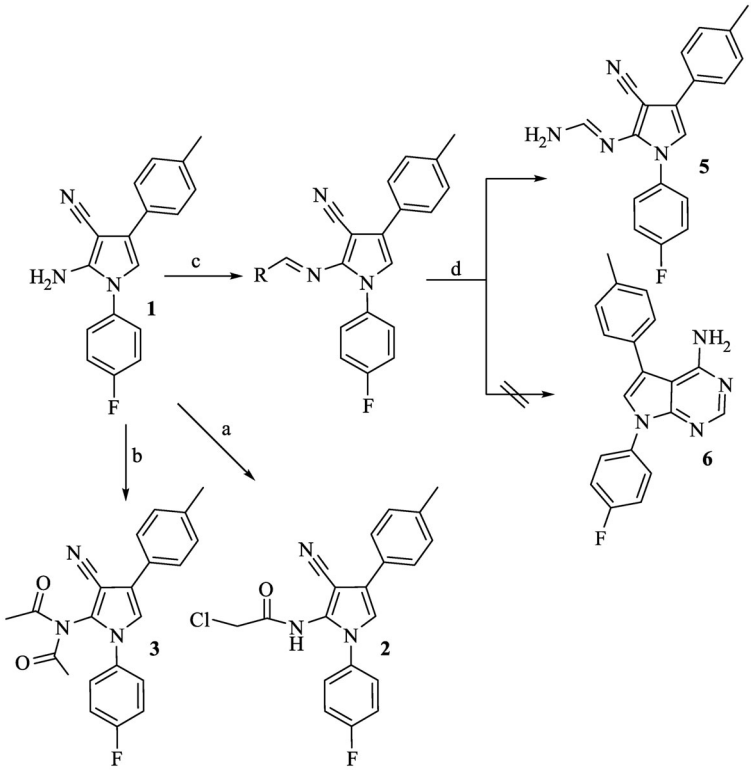
When the pyrrole-3-carbonitrile **1** was treated with chloroacetyl chloride at room temperature, the desired monoacetyl derivative **2** was obtained in 86% yield. Heating of **1** in a mixture of acetic acid–acetic anhydride for a short time afforded the unexpected diacetyl product **3** in 79% yield. Structural elucidation of products **2** and **3** was based on IR, ^{1}H NMR and mass spectroscopic determinations (see Experimental).

Hot treatment of **1** with trimethyl orthoformate or triethyl orthoformate provided the formimidates **4a** and **4b** in 79 and 86% yield, respectively. IR and ^{1}H NMR spectra accorded well the proposed structure of products **4** (Scheme 1).

The latter formimidates when reacted with saturated ethanolic ammonia solution at room temperature gave the (pyrrol-2-yl)formimidamide **5** in 85% yield, rather than the expected 7-deazaadenine **6**. ^{1}H NMR spectrum of **5** revealed NH_2 proton signals (broad) at $\delta \sim 2.38$ ppm (D_2O-exchangeable) which is absent in the spectra of their parents **4**. Mass spectrum of **5** showed a molecular ion peak *m/z* at 318 (100%). Noteworthy to mention that such method for the synthesis of product **5** has been previously reported for preparation of (*E*)-*N*′-(4-(3-(benzyloxy)phenyl)-3-cyano-1*H*-

pyrrol-2-yl)formimidamide form 2-amino-4-(3-(benzyloxy)phenyl)-1*H*-pyrrole-3-carbonitrile[8].

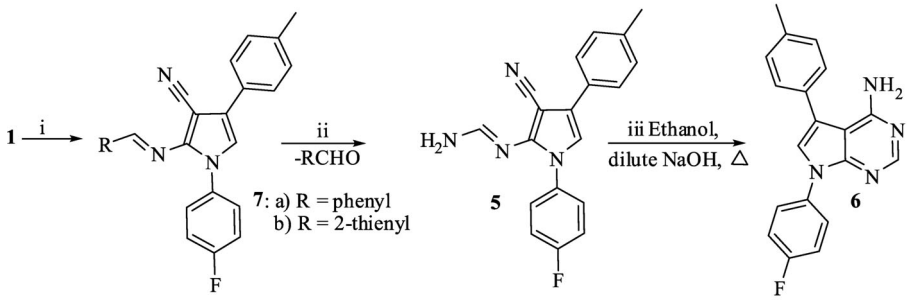
The 7-deazaadenine **6** was synthesized smoothly in 86% yield upon heating the pyrrolecarbonitrile **1** in formamide solution. Also, the interesting feature of *N*-arylidenamine fragment was used instead of the amino group of the pyrrole **1** to synthesize product **6**. Thus, when the corresponding 2-arylideneamino-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrole-3-carbonitrile derivatives **7b** (prepared from reaction of **1** with the desired aldehyde in 92 and 78.5% yield, respectively) were heated with formamide until formation of a precipitate and disappearance of the colored Schiff base afforded the



Reagents and conditions: a) chloroacetyl chloride, stirring at r.t., (86%); b) acetic acid/acetic anhydride mixture (1:1), heat, (79%); c) trimethyl- or triethyl orthoformate, heating, (79.9%); d) ethanolicammonia stirring for ~10 h at r.t., (85%)

SCHEME 1

N′-(3-cyano-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrol-2-yl)formimidamide (**5**) (m.p. and mixed m.p., 85% yield). Upon heating product **5** for 1 h in ethanol in the presence of alkaline catalyst, the 7-deazaadenine **6** was obtained (m.p. and mixed m.p., 67% yield) (Scheme 2).



Reagents and conditions: i) the desired aldehyde, dilute KOH solution (1–2 drops), warming for 5 min, (92 and 78.5%); ii) formamide, heating for ~1 h, (85%); iii) ethanol dilute NaOH, heat for 1 h, (67%)

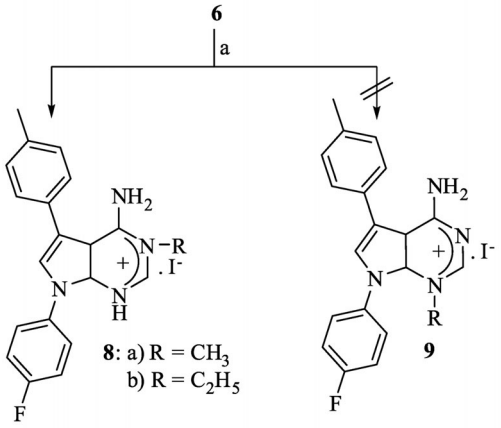
SCHEME 2

Structure of compound **6** was confirmed by studying of its IR, ^{1}H NMR and mass spectral determinations. Preparation of some 4-amino-6-aryl-5-cyanopyrrolo[2,3-*d*]pyrimidine derivatives has been reported from 2-(*N*-arylideneamino)-5-aryl-3,4-dicyanopyrrole and formamide at reflux temperature[9].

When the 7-deazaadenine **6** was treated with either methyl or ethyl iodide in hot DMF solution, the corresponding 3-alkylpyrrolopyrimidinium iodide salts **8a** and **8b** were afforded (62 and 50% yield, respectively), rather than the probable 1-alkylpyrrolopyrimidinium salts **9** (Scheme 3).

Comparison of the ^{13}C NMR spectra of **8** with that of the non-alkylated product **6** cleared that the signals due to C-2 and C-4 were down-field shifted (de-shielded). For example, these signals appeared in the case of compounds **8b** at 160.82 and 162.77 ppm, respectively (in case of compound **6** these signals were revealed, shielded at 152.30 and 157.52 ppm, respectively). Presumably, such noticeable shielding can be explained as being due to incorporation of the alkyl substituent at the N^3-position of the pyrrolo-pyrimidine ring, thus, supporting the proposed structure of type **8** rather than the probable structure of type **9**.

This finding accorded well with the previously reported observation for the ^{13}C NMR of some pyrimidinium and 1-methylpyrimidinium salts as well for some purinium and furo[2,3-*d*]pyrimidinium salts[10].



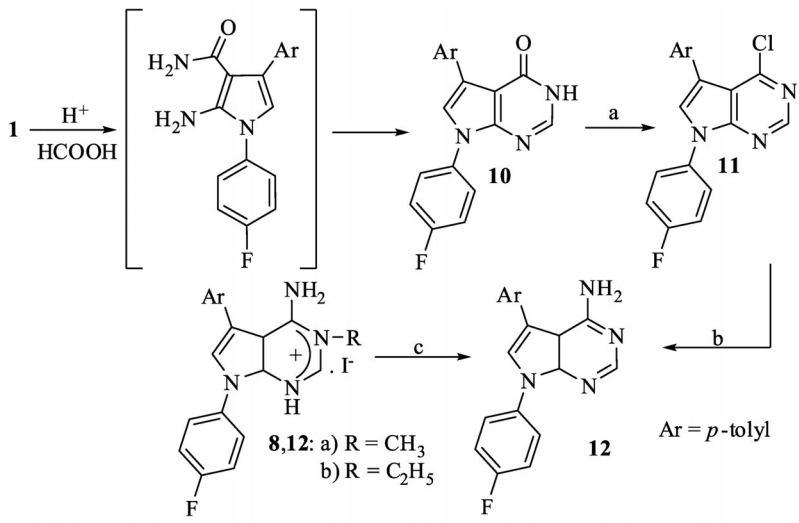
Reagents and conditions: a) alkyl halide, DMF, heating for 8 h, (62 and 50%)

SCHEME 3

In order to confirm and support the structure of the pyrroloprimidinium salts **8**, their dequaternization was tried. Thus, upon warming the iodide salts **8** in an ethanolic sodium hydroxide solution, their dequaternized and rearranged products *N*-alkylpyrrolo[2,3-*d*]pyrimidin-4-amines **12a** and **12b** were afforded in 49 and 79% yield, respectively. ^{1}H NMR and mass spectra of **12a** agreed its structure. The latter products were found to be identical (m.p. and mixed m.p.) with the products obtained from reactions of 4-chloro-7-(4-fluorophenyl)-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**11**) with methyl- or ethylamines in the presence of triethylamine as a catalyst. Product **11** was obtained in 81% yield from hot reaction of $POCl_3$ with pyrrolo[2,3-*d*]pyrimidin-4*H*-(7*H*)-one **10** (prepared in the present work via heating the starting pyrrolecarbonitrile **1** with formic acid, through a reaction believed to proceed through the formation of the corresponding 2-amino-3-carboxamidopyrrole followed by cyclization) (Scheme 4).

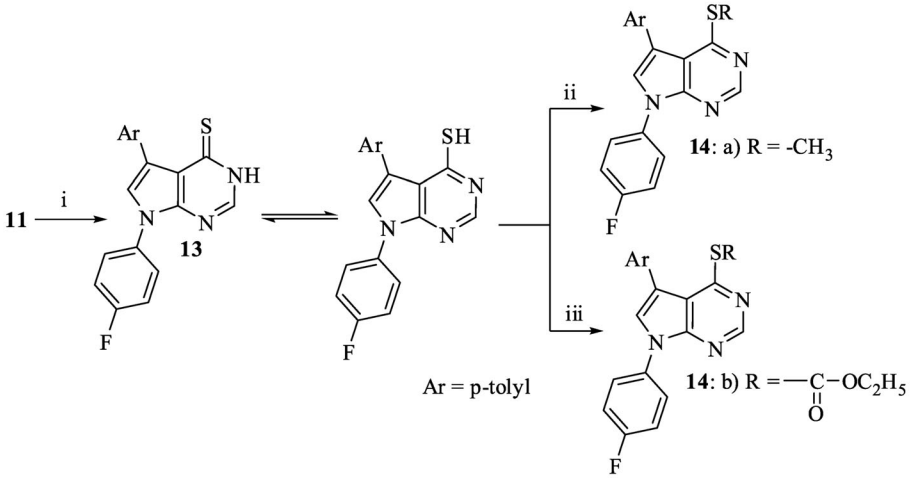
Mass spectra of the salts **8a** and **8b** exhibited molecular ion peaks *m/z* at 335 (25%) and 349 (13%), respectively, which corresponds to M^+ – HI. This observation suggested the splitting of HI in the mass spectrometer[11].

The present work was directed to probe reaction of 4-chloro-7-(4-fluorophenyl)-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**11**) with thiourea. Thus, when the 4-chloro product **11** was heated with thiourea in absolute ethanol, the thione **13** was readily obtained in 71% yield (see Experimental for structure confirmation data). Previously some thiopurine derivatives were obtained by treating chloropurines with thiourea[12] (Scheme 5).



Reagents and conditions: a) $POCl_3$, heat, (82%); b) desired aliphatic amine, ethanol, heat, (49 and 79%); c) ethanolic NaOH, warming

SCHEME 4

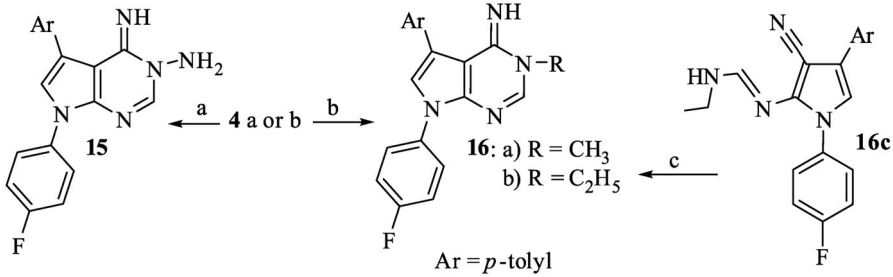


Reagents and conditions: i) thiourea, ethanl, short time heating, (71%); ii) dimethyl sulfate, alcoholic KOH, stirring at r.t. (72%); iii) ethyl chloroformate, benzene, KOH, stirring at r.t. (79%)

SCHEME 5

Reaction of the thione **13** with dimethyl sulfate in ethanol–KOH at room temperature provided the corresponding methylthio derivative **14a** in 72% yield. Meanwhile, its treatment with ethyl chloroformate in benzene at room temperature afforded the pyrrolo[2,3-*d*]pyrimidin-4-ylcarbonothioate **14b** in 79% yield.

In the present investigation, it was found that the formimidates **4a** or **4b** upon condensation with hydrazine hydrate–ethanol solution at room temperature ring closure occurred and the 4-iminopyrrolo[2,3-*d*]pyrimidin-3-amine **15** was obtained in 84% yield. Also, when the same reaction was repeated under the same conditions using either methyl- or ethylamine ring closure and alkylation at N-3 position of the pyrimidine ring of **4** occurred, affording 7-(4-fluorophenyl)-3-substituted-5-*p*-tolyl-3*H*-pyrrolo-[2,3-*d*]pyrimidin-4-(7*H*)-imines **16a** and **16b** in 80 and 60% yield, respectively. Worthy to note that only in the case of reaction of **4b** with ethylamine, the open chain product *N*′-(3-cyano-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrol-2-yl)-*N*-ethylformimidamide (**16c**) was separated and purified as a minor product (40% yield), which upon heating in sodium ethoxide–absolute ethanol solution for 5 h afforded product **16b** (m.p. and mixed m.p.) (Scheme 6).



Reagents and conditions: a) hydrazine hydrate/ethanol, stirring at r.t., (84%); b) methyl- or ethyl amine, ethanol, stirring at r.t., (60%); c) heating in NaOEt in absolute EtOH, 5 h

SCHEME 6

Structure of compounds **15** and **16** was elucidated on the basis of correct elemental analyses and spectral data (see Experimental).

Triazolo- and tetrazolopyrimidines are well known for their biological activities and exhibited in particular antitumor, hypotensive, antiseptic, antiarrhythmic and antiasthmatic properties, high affinity and selectivity for human adenosine A_3 receptor antagonists, and antibacterial and antifungal activities[13–15]. It has also been reported[16] that [1,2,4]triazolo-[4,3-*c*]pyrimidine derivatives could not be isolated even when the reaction

mixture was heated at a low temperature and can isomerize under different suitable conditions to the thermodynamically more stable [1,2,4]triazolo[1,5-*c*]. This isomerization can occur when [1,2,4]triazolo[4,3-*c*]pyrimidine derivative was treated with an acid or base, or thermally.

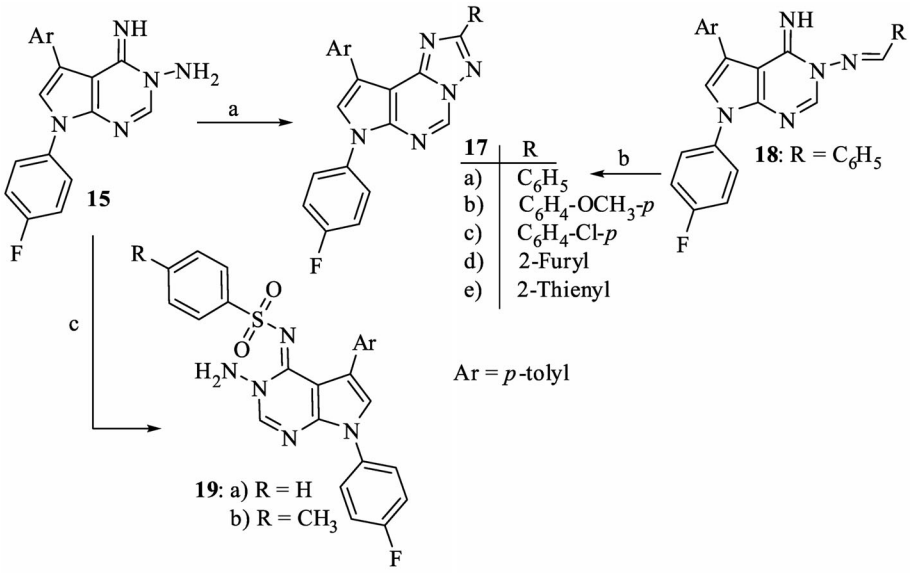
Therefore, the pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **17a–17e** were synthesized (81–62% yield) in the present work, when the imino compound **15** was left to react with some desired aldehydes in hot ethanol. Structure elucidation of products **17** based on correct elemental analyses and careful studying for their PMR and mass spectral determinations (see Experimental).

In the case of benzaldehyde reaction with the imino product **15**, the expected *N*-benzylidene derivative **18** was separated as by-product in 24% yield and identified. Structure of product **18** was confirmed from its IR and mass spectral determinations. Its UV spectrum indicated the presence of unsaturated chromophoric N=CH-Ph moiety in its structure. Also, when a pure sample of product **18** was heated in ethanol for 5 h, the imino product **17a** was afforded (m.p. and mixed m.p.). Some *N*-arylidene derivatives have been synthesized and characterized previously[17] from 6-amino-3-benzyl-7-imino-5-methyl-2,3,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidin-2-thione.

Due to the fact that the sulfonamide partial structure appears to belong to the so-called "privileged structures" in medicinal chemistry and it exhibits favorable pharmacokinetic properties including metabolic stability[18]. So, it was interesting to synthesize newer pyrrolo[2,3-*d*]pyrimidine derivatives incorporating sulfonamide moiety in their structure. Thus, when the imino product **15** reacted with either benzenesulfonyl- or 4-methylbenzenesulfonyl chloride in dry benzene, the corresponding benzene sulfonamides **19a** and **19b** were afforded in 73 and 79% yield, respectively, leaving the *N*-(3-amino) group intact (Scheme 7).

Structural assignment of the sulfonamides **19a** and **19b** was based on correct elemental analyses and spectroscopic determinations. IR spectra of the latter products exhibited NH_2 (amino and imino) stretching vibrations. ^{1}H NMR spectra of **19a** and **19b** (DMSO-d_6) displayed proton signals for CH_3, NH_2 and C_2-H, beside the aromatic proton signals and their mass spectra accorded well the proposed structures (see Experimental).

In the present work, synthesis of 7-(4-fluorophenyl)-9-*p*-tolyl-7*H*-pyrrolo-[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (**21**) was tried by two different routes. In the first route, the reaction between the chloro compound **11** and sodium azide in the presence of ammonium chloride and DMSO as a solvent afforded the tetrazolopyrimidine **21** in 90% yield. Ammonium chloride was used for in situ generation of ammonium azide. In the second route, the



Reagents and conditions: a) desired aldehyde, ethanol, heating for 12 h, (81–62%); b) ethanol, heating for 5 h; c) desired benzenesulfonyl chloride, dry benzene, stirring at r.t. (73 and 79%)

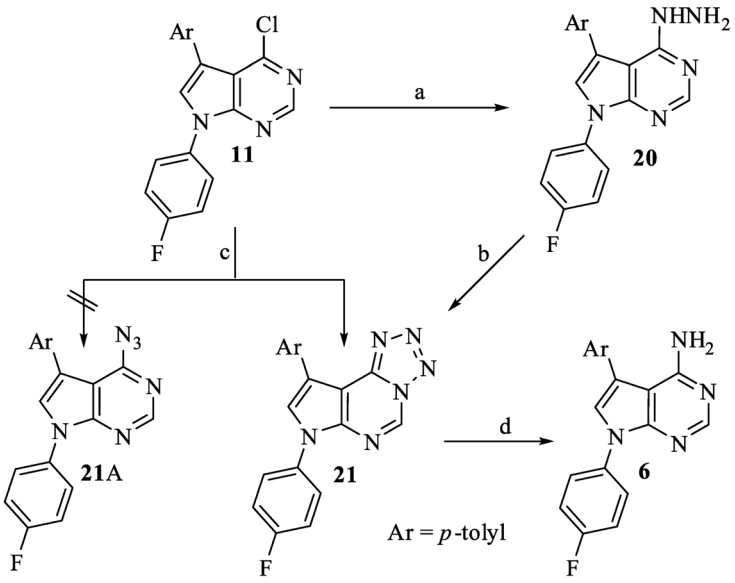
SCHEME 7

same tetrazole product **21** can also be obtained in 66% yield by diazotization of the hydrazide **20** (prepared from **11** and hydrazine hydrate in 93% yield) upon reaction with sodium nitrite in acetic acid while cooling (0–5 °C).

As the reactive cleavage of the tetrazole moiety constituted a synthetically important way for the preparation of amines, it was found that the 7-deazaadenine **6** was synthesized in 67% yield from the pyrrolotetrazolopyrimidine **21** employing activated zinc dusts in acetic acid as a reducing agent under boiling conditions. The amine **6** was identical with that obtained from reactions of either 2-amino-3-cyanopyrrole **1** or 2-arylideneamino-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrole-3-carbonitrile (**4**) with formamide (Scheme 8).

The absence of absorption in IR spectrum of **21** near 2100 cm^{-1} can exclude the possibility of the azide structure **21A** formation[19]. Also formation of the tetrazole **21** from the hydrazide **20** was supported by the absence of $NHNH_2$ functional group in its IR spectrum, which is clearly noticed in the spectrum of the hydrazide **20**. Mass spectrum of the tetrazole **21** showed regular fragmentation pattern giving a molecular ion peak *m/z* at 344 (35%) with the fragments at 316, 289 and 288, resulting due to successive elimina-

tion of nitrogen and hydrogen cyanide or subsequent elimination of two nitrogen molecules. ^{1}H NMR spectrum of **21** (DMSO-d_6) displayed resonances due to aromatic protons, CH_3 and C_2-H proton signals, respectively. Also, the spectrum revealed the absence of NH proton signals which were clearly displayed in the spectrum of the hydrazide **20**.



Reagents and conditions: a) hydrazine hydrate, ethanol, heat, (93%); b) sodium nitrite, acetic acid, cooling at 0–5 °C, (90%); c) sodium azide, ammonium chloride, DMSO, heat at 90 °C, (66%); d) acetic acid/Zn, boiling, (67%)

SCHEME 8

ANTIOXIDANT ACTIVITY

There is an increasing interest in antioxidants, particularly in those intended to prevent the presumed deleterious effects of free radicals in the human body, and to prevent the deterioration of fats and other constituents of foodstuffs. Antioxidants are defined as substances that when present at low concentrations compared with those of an oxidizable substrate significantly delay or prevent oxidation of that substrate. 1,1-Diphenyl-2-picrylhydrazyl (DPPH) is a stable free radical often used as a substance to evaluate the antioxidant capacity of an oxidant[20,21].

Results of Antioxidant Screening by DPPH Assay

The antioxidant activity of some selected pyrrole- and pyrrolo[2,3-*d*]-pyrimidine derivatives as measured by their ability to scavenge DPPH free radical is represented in Table I and Fig. 1. The obtained data showed that:

1) 2-Amino-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrole-3-carbonitrile (**1**) showed the best and highest scavenging activity (SA) (100%) at the concentration of 0.2 mg/ml as compared with ascorbic acid followed by the pyrrole-formimidate **4a** which showed SA 53.37%. Two other tested pyrrole derivatives **2** and **3** exhibited weak scavenging activity (27.10 and 7.28%). Apparently, the high SA gained by the pyrrolocarbonitrile **1** can be attributed to the presence and ability of the free NH_2 group to reduce free radical formation and to scavenge free radicals, meanwhile it is obvious that any substitution for this group lowers the gained antioxidant activity.

2) Pyrrolopyrimidine derivatives 7-(4-fluorophenyl)-5-*p*-tolyl-3*H*-pyrrole-[2,3-*d*]pyrimidin-4(7*H*)-one **10**, 7-(4-fluorophenyl)-4-hydrazinyl-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine **20** and 7-(4-fluorophenyl)-9-*p*-tolyl-7*H*-pyrrolo-[3,2-*e*]tetrazole[1,5-*c*]pyrimidine **21** were of similar high SA activity (100%) as ascorbic acid. Meanwhile, 7-(4-fluorophenyl)-4-(methylthio)-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**14a**) gained 52.34% SA activity. The tested pyrrolo[2,3-*d*]pyrimidine derivatives **8b** and **15** exhibited antioxidant activity lower than 50% (31.33–2.14%). Presumably, the remarkable antioxidant activities gained by products **10**, **20** and **21** could be perhaps due to the presence of NH (or NH_2) grouping in their structures.

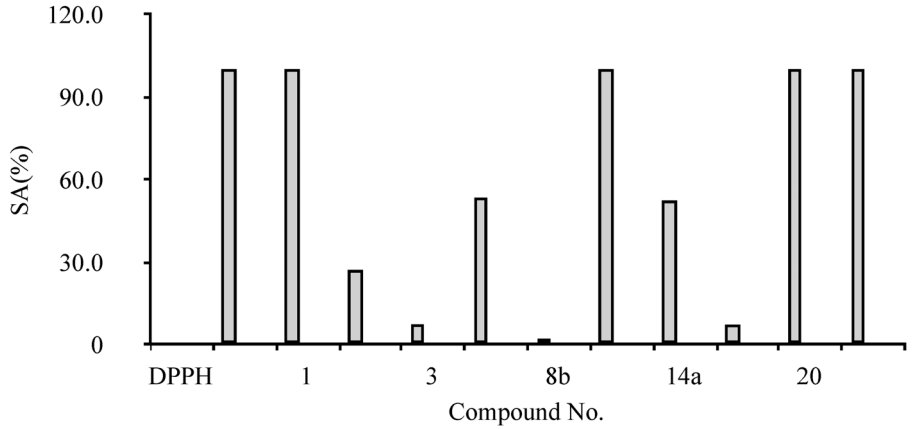


FIG. 1
Screening of antioxidant activity by the DPPH assay

TABLE I
Antioxidant activity of some pyrrole- and pyrrolopyrimidine derivatives

Compound	Concentration	Scavenging activity, %	Double integration area
DPPH	10^{-3} M of 1 mM ethanol	0	832413
	Pyrrole derivatives		
1	0.2	100	0
2	0.2	27.1	606772
3	0.2	7.28	771850
4a	0.2	53.37	3881218
	Pyrrolopyrimidine derivatives		
8b	0.2	2.14	814562
10	0.2	100	0
14a	0.2	52.34	397742
15	0.2	7.18	772659
20	0.2	100	0
21	0.2	100	0
Ascorbic acid	10^{-3} M/ 1 mM ethanol	100	0

So, the pyrrole **1** as well as the pyrrolo[2,3-*d*]pyrimidine derivatives **10**, **20** and **21** can be presented as potential "antioxidant candidate(s)", after carrying out, in the future, further necessary applications and precautions regarding to human health safety.

CONCLUSION

New pyrrole- and pyrrolo[2,3-*d*]pyrimidine derivatives, e.g. *N*′-(3-cyano-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrol-2-yl)formimidamide, pyrrolepyrimidine-4-amine, 3-alkylpyrrolopyrimidinium iodide salts, *N*-alkylpyrrolo-[2,3-*d*]pyrimidin-4-amines, 7-(4-fluorophenyl)-5-*p*-tolyl-3*H*-pyrrolo[2,3-*d*]-pyrimidin-4(7*H*)-thione, 7-(4-fluorophenyl)-4-(methylthio)-5-*p*-tolyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine and *O*-ethyl-*S*-7-(4-fluorophenyl)-5-*p*-tolyl-7*H*-pyrrolo-[2,3-*d*]pyrimidin-4-ylcarbonothioate were synthesized and characterized. Several examples of the synthesized compounds showed high to remarkable

antioxidant scavenging activity, compared to ascorbic acid, as measured by their ability to scavenge the DPPH free radical.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were carried out by the Micro analytical Laboratory, National Research Center, Cairo, Egypt. IR spectra (KBr-disc; ν in cm^{-1}) were recorded using a Jasco FT/IR-6100 spectrophotometer. UV-Vis spectra were recorded in methanol on a Schimadzu UV-visible recoding spectrophotometer 240. ^1H and ^{13}C NMR spectra (δ in ppm, *J* in Hz) were recorded in DMSO-d_6 using a Varian mercury or a Varian Gemini with chemical shift in δ from Me_4Si. Mass spectra were recorded on a GC/MS finnigan SSQ 7000(EIev70) spectrophotometer. Antioxidant screening was carried out using a Brucker ELEXSYS-E500 electron paramagnetic spectrometer (Central Laboratory Services unite, National Research Center, Cairo, Egypt) at room temperature; conditions used: microwave frequency 9.77 GHz, microwave power 2 mW, modulation amplitude 4.0 G, receiver gain 60 db, and sweep time 20.97 s. The antioxidant activity of the selected compound was assessed by measuring the ability of each compound to scavenge the free radical of 1,1-diphenyl-2-picrylhydrazyl (DPPH) using electron spin resonance (ESR) spectroscopy[22].

Blank probe was obtained by mixing 10^{-3} M of 1 mM ethanol solution of DPPH and 10^{-3} M/1 ml ethanol (as control solution containing no antioxidant). Standard solution was prepared from Vitamin C (as a standard) with concentration 10^{-3} M/1 mM ethanol. Both the test compounds solutions and the standard was added to 10^{-3} M of 1 mM ethanol solution of DPPH (stock) to initiate the antioxidant–radical reaction. The concentration of the investigated compound was 0.2 mg/ml ethanol. After that the mixture was stirred for 1 min, transferred to a quartz flat cell ER-160ft and analyzed by ESR spectroscopy. ESR signal of DPPH in methanol usually appears at $g = 2.006$ characterizing the free radical. The decrease of this signal after mixing with the solution of each compound is taken as indication of the antioxidant activity, measured as a double integration area (DIA).

$$\% \text{ Activity} = \frac{[\text{DIA (DPPH)} - \text{DIA (DPPH + Compound)}] \times 100}{\text{DIA (DPPH)}}$$

The scavenging activity (SA) of each investigated compound and Vitamin C was estimated by comparing the DPPH signals in the antioxidant–radical reaction mixture and the control reaction at the same time, and expressed percentage DPPH remaining. The DPPH-radical scavenging activity of the investigated compound and Vitamin C was calculated using the formula: $SA = 100 \times (A_0 - A_x)/A_0$ [%], where A_x and A_0 are the double-integral ESR for the first line of samples in the presence and absence of test compounds, respectively.

2-Amino-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrole-3-carbonitrile (**1**)

To a solution of 2-(4-fluorophenylamino)-1-*p*-tolylethanone (7 g, 0.027 mol) in absolute ethanol (80 ml), malononitrile (2 g, 0.03 mol) was added and the mixture was heated under reflux while stirring, then sodium ethoxide (2.7 g) in absolute ethanol (50 ml) was added dropwise to the reaction mixture. The whole mixture was heated under reflux for 3 h. The solid product separated out after cooling was filtered off, washed with cold water, dried and crystallized to give **1** as brown crystals (ethanol), yield 4.5 mg, m.p. 154–156 °C. IR: 3421,

3337 (NH_2), 2196 (C≡N). For $C_{18}H_{14}FN_3$ (291.32) calculated: 74.21% C, 4.84% H, 14.42% N; found: 74.01% C, 4.65% H, 14.51% N.

2-Chloro-*N*-(3-cyano-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrol-2-yl)acetamide (**2**)

To a stirred solution of pyrrole **1** (0.01 mol) in dioxane (20 ml) containing few drops of triethylamine, chloroacetylchloride was added dropwise. Stirring was continued for 5 h. The reaction mixture was poured onto crushed ice. The obtained solid product was filtered, dried and crystallized to give **2** as white crystals (methanol), m.p.178–180 °C, yield 86%. IR: 3180 (NH), 2229 (C≡N), 1676 (C=O). ^{1}H NMR (200 MHz): 2.35 (s, 3 H, CH_3), 4.26 (s, 2 H, CH_2), 7.27–7.63 (m, 9 H, ArH), 10.54 (b, 1 H, NH, D_2O-exchangeable). For $C_{20}H_{15}ClFN_3O$ (367.80) calculated: 65.31% C, 4.11% H, 11.42% N; found: 65.42% C, 4.20% H, 11.60% N.

N-Acetyl-*N*-(3-cyano-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrol-2-yl)acetamide (**3**)

A solution of **1** (0.01 mol) in mixture of acetic acid (10 ml) and acetic anhydride (40 ml) was heated under reflux for 6 h. Left to cool, the reaction mixture was poured onto crushed ice. The obtained solid product was filtered, dried and crystallized to give **3** as white crystals (methanol), m.p. 140–142 °C, yield 79%. IR: 2222 (C≡N), 1725 (C=O). MS, *m/z* (%): 375 (M, 30), 377 (3), 292 (100). ^{1}H NMR (270 MHz): 2.27 (s, 6 H, 2 CH_3), 2.37 (s, 3 H, CH_3), 7.31–7.80 (m, 9 H, ArH and C_5-H). For $C_{22}H_{18}FN_3O_2$ (375.40) calculated: 70.39% C, 4.83% H, 11.9% N; found: 69.91% C, 4.67% H, 10.98% N.

Alkyl *N*-3-Cyano-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrol-2-ylformimidate (**4**).
General Method

To a solution of **1** (0.01 mol) in methyl (or ethyl) orthoformate (30 ml), trifluoroacetic acid (0.5 ml) was added. The reaction mixture was heated under reflux for 3 h. Left to cool, the obtained solid product was filtered and crystallized from the proper solvent to give **4a** and **4b**.

Methyl N-3-cyano-1-(4-fluorophenyl)-4-p-tolyl-1H-pyrrol-2-ylformimidate (**4a**): Yellowish crystals (methanol), m.p. 152–154 °C, yield 79%. IR: 2214 (C≡N), 1635 (C=N). ^{1}H NMR (200 MHz): 2.34 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 7.24 (d, 2 H, J = 8.0, ArH), 7.34–7.45 (m, 5 H, ArH), 7.61 (d, 2 H, J = 7.6, ArH), 8.6 (s, 1 H, CH=N). For $C_{20}H_{16}FN_3O$ (333.36) calculated: 72.06% C, 4.84% H, 12.61% N; found: 72.20% C, 4.76% H, 12.54% N.

Ethyl N-3-cyano-1-(4-fluorophenyl)-4-p-tolyl-1H-pyrrol-2-ylformimidate (**4b**): Yellowish crystals (methanol), m.p. 138–140 °C, yield 86%. IR: 2210 (C≡N), 1631 (C=N). MS, *m/z* (%): 347 (45.4), 290 (22.9), 155 (52.9), 95 (100). For $C_{21}H_{18}FN_3O$ (347.39) calculated: 72.61% C, 5.22% H, 12.10% N; found: 72.67% C, 5.32% H, 12.24% N.

N′-(3-Cyano-1-(4-fluorophenyl)-4-*p*-tolyl-1*H*-pyrrol-2-yl)formimidamide (**5**)

To a suspension of **4a** or **4b** (0.01 mol) in ethanol (30 ml), ammonia solution (5 ml, 33%) was added. The reaction mixture was stirred at room temperature for 10 h. The obtained precipitate was filtered and crystallized to give **5** as yellow crystals (ethanol), m.p. 188–190 °C, yield 85%. IR: 3396, 3331 (NH_2), 2197 (C≡N), 1677 (C=N). ^{1}H NMR (270 MHz): 2.32 (s, 3 H, CH_3), 2.38 (s, 2 H, NH_2, D_2O-exchangeable), 7.16–7.66 (m, 9 H, ArH), 8.21 (s,

1 H, CH=N). MS, *m/z* (%): 319 (M^+, 41), 318 (M, 100), 94.93 (39). For $C_{19}H_{15}FN_4$ (318.35) calculated: 71.68% C, 4.75% H, 17.60% N; found: 71.66% C, 4.80% H, 17.45% N.

7-(4-Fluorophenyl)-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**6**)

Method A. A solution of **1** (0.01 mol) in formamide (30 ml) was heated under reflux for 3 h and left to cool. The obtained solid product was filtered and crystallized to give **6**.

Method B. A mixture of **7a** or **7b** (0.01 mol) and formamide (20 ml) was heated under reflux until the color of the Schiff base **7** disappeared and a precipitate was formed. The precipitate was filtered and purified to give clean cut of **5** as an intermediate product (m.p. and mixed m.p.). Upon heating the product **5** in ethanol for 1 h in the presence of few drops of dilute NaOH, the reaction mixture was left to cool, the obtained solid product was filtered and crystallized to give **6** (m.p. and mixed m.p.).

Method C. The tetrazole **21** (0.01 mol) was dissolved in glacial acetic acid (10 ml), zinc powder (0.5 g) was added portion-wise while stirring over a period of 30 min (an exothermic reaction was observed). After complete addition, the reaction mixture was heated under reflux for 4 h. Left to cool and poured onto crushed ice. The resulting mixture was neutralized (to pH 7) with 6 M ammonia solution and extracted with chloroform (2 × 30 ml). The total chloroform layer was dried over anhydrous magnesium sulfate, concentrated under vacuum and cooled to give **6** as pale brown crystals (ethanol), m.p. 178–180 °C, yield 86% (method *A*), 80% (method *B*) and 67% (method *C*), respectively. IR: 3471, 3281 (NH_2), 1630 (C=N). ^{1}H NMR (270 MHz): 2.38 (s, 3 H, CH_3), 6.23 (b, 2 H, NH_2), 7.31–7.94 (m, 9 H, Ar-H and C_6-H), 8.21 (s, 1 H, C_2-H). ^{13}C NMR (270 MHz): 152.30 (C2), 157.52 (C4), 100.77 (C4a), 136.29 (C7a), 20.74 (CH_3-tolyl), 115–133.79 (C5, C6, aromatics). MS, *m/z* (%): 319 (M^+, 20), 318 (M, 100). For $C_{19}H_{15}FN_4$ (318.35) calculated: 71.68% C, 4.75% H, 17.60% N; found: 71.60% C, 4.77% H, 17.55% N.

Reaction of the Pyrrolecarbonitrile **1** with Benzaldehyde and 2-Thiophenealdehyde. General Method

To a mixture of **1** (0.01 mol) and the desired aldehyde (0.01 mol) in absolute ethanol (20 ml), 1 ml KOH solution (1%) was added. The reaction mixture was warmed for 15 min. Left to cool, the obtained solid product was filtered to give **7a** or **7b**.

2-(Benzylideneamino)-1-(4-fluorophenyl)-4-p-tolyl-1H-pyrrole-3-carbonitrile (**7a**): Yellow crystals (cyclohexane), m.p. 210–212 °C, yield 92.9% (1.3 g). IR: 2207 (C≡N), 1613 (C=N). For $C_{25}H_{18}FN_3$ (379.43) calculated: 79.14% C, 4.78% H, 11.07% N; found: 79.22% C, 4.88% H, 11.23% N.

(4-Fluorophenyl)-2-(thiophen-2-ylmethyleneamino)-4-p-tolyl-1H-pyrrole-3-carbonitrile (**7b**): Yellow crystals (cyclohexane), m.p. 220–222 °C, yield 78.57% (1.1 g). IR: 2203 (C≡N), 1627 (C=N), 1590 (C=C). For $C_{23}H_{16}FN_3S$ (385.46) calculated: 71.67% C, 4.18% H, 10.90% N, 8.32% S; found: 71.65% C, 4.23% H, 11.00% N, 8.35% S.

Reaction of the Pyrrolopyrimidin-4-amine **6** with Alkyl Halides. General Method

A mixture of **6** (0.01 mol) and the desired alkyl halides (methyl or ethyl iodide) (0.01 mol) in dimethylformamide (10 ml) was heated under reflux for 8 h. Excess solvent was evaporated under reduced pressure. The remaining residue was triturated with drops of methanol–

acetone mixture. The obtained solid product was filtered, dried and crystallized from methanol to give **8a** or **8b**.

7-(4-Fluorophenyl)-3-methyl-5-p-tolyl-2,3,4,7-tetrahydro-1H-prrolo[2,3-d]primidin-4-amine, Iodide Salt (**8a**): Pale brownish crystals (methanol), m.p. 242–244 °C, yield 62%. IR: 3417, 3259 (NH_2), 1656 (C=N). ^{1}H NMR (500 MHz): 2.37 (s, 3 H, CH_3), 2.40 (s, 3 H, N-CH_3), 7.27 (m, 7 H, ArH), 7.73–7.75 (m, 2 H, ArH), 8.00 (s, 1 H, CH-pyrimidine), 8.34 (b, 2 H, NH_2). MS, *m/z* (%): 335 [M^+ – HI (25)], 332 (87), 331 (100), 318 (48), 317 (26), 291 (8), 127 (11). For $C_{20}H_{18}FIN_4^-$ (463.31) calculated: 51.85% C, 4.57% H, 12.09% N; found: 51.44% C, 4.33% H, 12.20% N.

3-Ethyl-7-(4-fluorophenyl)-5-p-tolyl-2,3,4,7-terahydro-1H-pyrrolo[2,3-d]pyrimidin-4-amine, Iodide Salt (**8b**): Pale brownish crystals (methanol), m.p. 247–249 °C, yield 50%. IR: 3345 (NH_2), 2951, 2920 (CH-aliphatic), 1626 (C=N). ^{1}H NMR (500 MHz): 1.33 (t, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 4.27 (q, 2 H, CH_2), 7.31–7.78 (m, ArH, NH_2), 7.33 (s, 1 H, CH-pyrrole), 8.52 (s, 1 H, C-2). ^{13}C NMR (500 MHz): 160.82 (C2), 162.77 (C4), 100.54 (C4a), 146.24 (C5), 151.21 (C7a), 14.03 (CH_3-ethyl), 21.24 (CH_3-tolyl), 39.50 (CH_2-ethyl), 116.73–138.52 (C6, aromatics). MS, *m/z* (%): 349 [M^+ – HI (13)], 348 (15), 347 (62), 350 (24), 318 (base peak, 100). For $C_{21}H_{20}FIN_4^-$ (477.34) calculated: 52.84% C, 4.86% H, 11.74% N; found: 53.16% C, 4.68% H, 11.7 4% N.

7-(4-Fluorophenyl)-5-*p*-tolyl-3*H*-pyrrolo[2,3-*d*]pyrimidin-4(7*H*)-one (**10**)

A solution of **1** (0.01 mol) in formic acid (20 ml) was heated under reflux for 3 h and then allowed to cool. The reaction mixture was poured onto crushed ice. The obtained solid product was filtered, dried and crystallized to give **10** as buff crystals (ethanol–DMF 2:1 v/v), m.p. > 250 °C, yield 86%. IR: 3232 (NH), 1651 (C=O). ^{1}H NMR (200 MHz): 2.32 (s, 3 H, CH_3), 7.15 (d, 2 H, *J* = 8.0, ArH), 7.38 (m, 2 H, ArH), 7.71 (s, 1 H, CH-pyrrole), 7.79 (m, 2 H, ArH), 7.91 (d, 2 H, *J* = 7.6, ArH), 7.98 (s, 1 H, H-2), 12.16 (b, 2 H, NH, D_2O-exchangeable). MS, *m/z* (%): 320 (22), 319 (M^+, 100), 318 (75). For $C_{19}H_{14}FN_3O$ (319.33) calculated: 71.46% C, 4.42% H, 13.16% N; found: 71.37% C, 4.51% H, 13.22% N.

4-Chloro-7-(4-fluorophenyl)-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**11**)

A solution of **10** (0.01 mol) in $POCl_3$ (20 ml) was heated under reflux for 3 h and then allowed to cool. The reaction mixture was poured onto crushed ice. The obtained solid product was filtered, dried and crystallized to give **11** as colorless crystals (methanol), m.p. 162–164 °C, yield 81%. IR: 1587 (C=N), 1535 (C=C). MS, *m/z* (%): 340 (6), 339 ($M^{\bullet+}$, 29), 337 (29), 336 (100). For $C_{19}H_{13}ClFN_3$ (337.78) calculated: 67.56% C, 3.88% H, 12.44% N; found: 67.40% C, 3.76% H, 12.51% N.

Reaction of the 4-Chloro Product **11** with Primary Aliphatic Amines

Method A. To a mixture of **11** (0.01 mol) and methyl- or ethylamine (0.01 mol) in ethanol (25 ml), few drops of triethylamine were added. The reaction mixture was heated under reflux for 6 h, concentrated and left to cool. The obtained solid product was filtered and crystallized to give **12a** or **12b**.

Method B. To a solution of **8a** or **8b** (0.82 g, 0.0025 mol) in aqueous ethanol (100 ml, 50%), sodium hydroxide solution (2 ml, 4%) was added. The reaction mixture was heated (water-bath temperature) for 3 h and left to cool. The obtained solid product was filtered

off, washed with water and crystallized from ethanol to give product **12a** or **12b** (m.p. and mixed m.p. with the products obtained from method *A* gave no depression).

7-(4-Fluorophenyl)-N-methyl-5-p-tolyl-7H-pyrrolo[2,3-d]pyimidin-4-amine (**12a**): Colorless crystals (ethanol), m.p. 126–128 °C, yield 49% (0.7 g). IR: 3403 (NH), 1592 (C=N). ^{1}H NMR (270 MHz): 2.38 (s, 3 H, CH_3), 2.94 (s, 3 H, N-CH_3), 5.6 (b, 1 H, NH), 7.31–7.46 (m, 6 H, ArH), 7.63 (s, 1 H, CH-pyrrole), 7.88–7.91 (m, 2 H, ArH), 8.29 (s, 1 H, H-2). For $C_{20}H_{17}FN_4$ (332.37) calculated: 72.27% C, 5.16% H, 16.86% N; found: 72.31% C, 5.20% H, 16, 90% N.

N-Ethyl-7-(4-fluorophenyl)-5-p-tolyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**12b**): Colorless crystals (ethanol), m.p. 138–140 °C, yield 79.5% (0.65 g). IR: 3437 (NH), 1590 (C=N), 1543 (C=C). ^{1}H NMR (500 MHz): 1.09 (t, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 3.45 (q, 2 H, CH_2), 5.51 (b, 1 H, NH), 7.42 (s, 1 H, CH-pyrrole), 7.30–7.62 (m, ArH), 8.23 (s, 1 H, C-2). MS, *m/z* (%): 346 (M, 96), 276 (29), 122 (43), 95 (100). For $C_{21}H_{19}FN_4$ (346.40) calculated: 72.81% C, 5.53% H, 216.17% N; found: 72.75% C, 5.62% H, 16.21% N.

7-(4-Fluorophenyl)-5-*p*-tolyl-3*H*-pyrrolo[2,3-*d*]pyrimidin-4(7*H*)-thione (**13**)

A mixture of **11** (0.01 mol) and thiourea (0.01 mol) in absolute ethanol (30 ml) was heated under reflux for 2 h and then left to cool. The obtained solid product was filtered and crystallized to give the thione **13** as yellowish crystals (ethyl acetate), m.p. 272–274 °C, yield 71%. IR: 3127 (NH), 1577 (C=N), 1550 (C=C), 1442, 1353, 1207 (C=S). MS, *m/z* (%): 336 (16.30), 335 (M, 51), 334 (100). For $C_{19}H_{14}FN_3S$ (335.40) calculated: 68.04% C, 4.21% H, 12.53% N, 9.56% S; found: 68.10% C, 4.23% H, 12.58% N, 9.63% S.

7-(4-Fluorophenyl)-4-(methylthio)-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**14a**)

To a suspension of **13** (0.83 g, 0.0025 mol) in ethanol (10 ml) and KOH solution (2 ml water containing 0.0125 mol KOH), dimethyl sulfate (0.0025 mol) was added. The reaction mixture was stirred at room temperature (~25 °C) for 4 h. The obtained precipitate was filtered off, washed with water and crystallized to give **14a** as colorless crystals (ethanol), m.p. 136–138 °C, yield 72.3% (0.6 g). IR: 1579 (C=N), 1540 (C=C). MS, *m/z* (%): 349 (M, 100), 350 (22). ^{1}H NMR (270 MHz): 2.36 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 7.0–7.91 (m, 9 H, ArH and CH-pyrrole), 8.67 (s, 1 H, C_2-H). For $C_{20}H_{16}FN_3S$ (349.42) calculated: 68.75% C, 4.62% H, 12.03% N, 9.18% S; found: 68.70% C, 4.58% H, 12.20% N, 9.22% S.

O-Ethyl *S*-7-(4-Fluorophenyl)-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylcarbonothioate (**14b**)

To a suspension of **13** (0.83 g, 0.0025 mol) in benzene (10 ml) and KOH solution (2 ml water containing 0.0125 mol KOH), ethyl chloroformate (0.0025 mol) was added. The reaction mixture was stirred at room temperature (~25 °C) for 4 h. The obtained precipitate was filtered off, washed with water and crystallized to give **14b** as colorless crystals (ethanol), m.p. 132–134 °C, yield 79.5% (0.66 g). IR: 1718 (C=O), 1578 (C=N), 1515 (C=C). ^{1}H NMR (500 MHz): 1.33 (t, 3 H, CH_3), 3.87 (q, 2 H, CH_2), 7.13–7.92 (m, ArH), 7.93 (s, CH-pyrrole), 8.85 (s, 1 H, C-2). MS, *m/z* (%): 408 (M^+, 17), 407 (7), 334 (24), 171 (15), 122 (16). For $C_{22}H_{18}FN_3O_2S$ (407.46) calculated: 64.85% C, 4.45% H, 10.31% N, 7.87% S; found: 64.90% C, 4.51% H, 10.38% N, 7.90% S.

7-(4-Fluorophenyl)-4-imino-5-*p*-tolyl-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-3-amine (**15**)

To a suspension of the formimidate **4a** or **4b** (0.01 mol) in ethanol (50 ml), hydrazine hydrate (0.012 mol) was added. The reaction mixture was stirred at room temperature for 5 h. The obtained precipitate was filtered and crystallized to give **15** as colorless crystals (benzene), m.p. 156–160 °C, yield 84%. IR: 3324, 3290, 3140 (NH, NH_2), 1629 (C=N). ^{1}H NMR (300 MHz): 2.3 (s, 3 H, CH_3), 5.6 (s, 2 H, N-NH_2, D_2O-exchangeable), 6.8 (b, 1 H, NH, D_2O-exchangeable), 7.2–7.8 (m, 9 H, ArH and CH-pyrrole), 8.2 (s, 1 H, C_2-H). For $C_{19}H_{16}FN_5$ (333.36) calculated: 68.46% C, 4.84% H, 21.015% N; found: 68.50% C, 4.73% H, 21.22% N.

7-(4-Fluorophenyl)-3-methyl-5-*p*-tolyl-3*H*-pyrrolo[2,3-*d*]pyrimidin-4(7*H*)-imine (**16a**)

To a stirred suspension of **4a** or **4b** (0.01 mol) in ethanol (50 ml), methylamine (0.01 mol) was added. The stirring was continued at room temperature for 15 h. The obtained precipitate was filtered and crystallized to give **16a** as colorless crystals (methanol–few drops of water), m.p. 162–164 °C, yield 80% (0.8 g). IR: 3326 (NH), 1628 (C=N). ^{1}H NMR (270 MHz): 2.37 (s, 3 H, CH_3), 3.4 (s, 3 H, CH_3), 6.5 (1 H, s, NH), 7.27–7.75 (m, 9 H, ArH and CH-pyrrole), 8.0 (s, 1 H, C_2-H). MS, *m/z* (%): 333 (M^{+1}, 27), 332 (M, 82), 331 (100). For $C_{20}H_{17}FN_4$ (332.37) calculated: 72.27% C, 5.16% H, 16.86% N; found: 72.34% C, 5.10% H, 16.72% N.

Synthesis of **16b** and **16c**

To a suspension of **4a** or **4b** (0.01 mol) in ethanol (50 ml), ethylamine (0.01 mol) was added and the reaction mixture was stirred at room temperature (~25 °C) for 15 h. The obtained precipitate was filtered and purified by chromatographic TLC plate (eluent: petroleum ether–ethyl acetate 2:1) and crystallized to give **16b** (major) and **16c** (minor).

3-Ethyl-7-(4-fluorophenyl)-5-p-tolyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-imine (**16b**): Colorless crystals (ethanol), m.p. 160–162 °C, yield 60.3% (0.55 g). IR: 3345 (NH), 1626 (C=N), 1514 (C=C). MS, *m/z* (%): 347 (M^+, 11), 346 (M, 100), 318 (83). For $C_{21}H_{19}FN_4$ (346.40) calculated: 72.81% C, 5.53% H, 16.17% N; found: 72.77% C, 5.49% H, 16.33% N.

N′-(3-Cyano-1-(4-fluorophenyl)-4-p-tolyl-1H-pyrrol-2-yl)-N-ethylformimidamide (**16c**): Colorless crystals (ethanol), m.p. 138–140 °C, yield 40% (0.35 g). IR: 3346 (NH), 2199 (C≡N), 1617 (C=N). ^{1}H NMR (500 MHz): 1.16 (t, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 3.15 (q, 2 H, CH_2), 2.05 (s, 1 H, NH), 7.19 (s, 1 H, pyrrole), 7.15–7.54 (ArH and N=CH). MS, *m/z* (%): 346 (M, 73), 94 (100). For $C_{21}H_{19}FN_4$ (346.40) calculated: 72.81% C, 5.53% H, 16.17% N; found: 72.83% C, 5.55% H, 16.21% N.

Cyclization of **16c** to **16b**

To a solution of **16c** (0.01 mol) in absolute ethanol (20 ml), sodium ethoxide solution (0.5 g Na metal dissolved in 7 ml of absolute ethanol) was added. The reaction mixture was heated under reflux for 5 h and left to cool. The obtained solid product was filtered and crystallized from benzene–methanol (1:2) to give **16b** (m.p. and mixed m.p. no depression).

2-(4-Aryl)-7-(4-fluorophenyl)-9-*p*-tolyl-7*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **17a–17e**

A mixture of **15** (0.01 mol) and the desired aldehyde (0.01 mol) in absolute ethanol (30 ml) was heated under reflux for 12 h and then left to cool. The obtained solid product was filtered to give **17a–17e**.

7-(4-Fluorophenyl)-2-phenyl-9-p-tolyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**17a**): White powder (benzene), m.p. 252–254 °C, yield 68% (1.1 g). IR: 1625 (C=N), 1514 (C=C). MS, *m/z* (%): 419 (M, 100), 420 (19), 95 (4), 77 (2.65). UV-Vis: 267 nm (ε 37 453). For $C_{26}H_{18}FN_5$ (419.45) calculated: 74.45% C, 4.33% H, 16.70% N; found: 74.39% C, 4.45% H, 17.00% N.

7-(4-Fluorophenyl)-2-(4-methoxyphenyl)-9-p-tolyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**17b**): White powder (benzene), m.p. 230–232 °C, yield 81%. IR: 1639 (C=N), 1612 (C=C). MS, *m/z* (%): 450 (35), 449 (M^+, 100), 318 (23), 317 (12.9), 224 (17). For $C_{27}H_{20}FN_5O$ (449.48) calculated: 72.15% C, 4.48% H, 15.58% N; found: 72.34% C, 5.51% H, 15.66% N.

2-(4-Chlorophenyl)-7-(4-fluorophenyl)-9-p-tolyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**17c**): Colorless crystals (benzene), m.p. 258–260 °C, yield 75% (1.2 g). IR: 1626 (C=N), 1513 (C=C). ^{1}H NMR (200 MHz): 2.4 (s, 3 H, CH_3), 7.35–8.42 (m, 13 H, ArH and CH-pyrrole), 9.53 (s, 1 H, C_2-H). UV-Vis: 267 nm (ε 37 037). For $C_{26}H_{17}ClFN_5$ (453.90) calculated: 68.80% C, 3.78% H, 15.43% N; found: 69.00% C, 3.82% H, 15.29% N.

7-(4-Fluorophenyl)-2-(furan-2-yl)-9-p-tolyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**17d**): Brownish white crystals (benzene), m.p. 220–222 °C, yield 62%. IR: 1630 (C=N), 1555 (C=C). ^{1}H NMR (200 MHz): 2.4 (s, 3 H, CH_3), 6.76 (s, 1 H, C_4-H furyl), 7.3–8.3 (m, 11 H, ArH, C_6-H and C_3-H, C_5-H furyl), 9.5 (s, 1 H, C_2-H). For $C_{24}H_{16}FN_5O$ (409.42) calculated: 70.41% C, 3.94% H, 17.11% N; found: 70.54% C, 4.00% H, 17.35% N.

7-(4-Fluorophenyl)-2-(thiophen-2-yl)-9-p-tolyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine **17e**: Pale brown crystals (benzene), m.p. 222–224 °C, yield 81%. IR: 1623 (C=N), 1559 (C=C). ^{1}H NMR (200 MHz): 2.32 (s, 3 H, CH_3), 7.2 (s, 1 H, CH-pyrrole), 7.25–7.9 (m, Ar-H), 9.45 (s, 1 H, C-2). MS, *m/z* (%): 425 (M, 16), 343.94 (28%), 318 (75), 308 (100). For $C_{24}H_{16}FN_5S$ (425.48) calculated: 67.75% C, 3.79% H, 16.46% N, 7.54% S; found: 67.80% C, 3.83% H, 16.60% N, 7.66% S.

N-Benzylidene-7-(4-fluorophenyl)-4-imino-5-*p*-tolyl-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-3-amine (**18**)

A mixture of 15 (1.64 g, 0.005 mol) and benzaldehyde (0.005 mol) in absolute ethanol (20ml) was heated under reflux for 10 h and left to cool. The obtained solid product was filtered off to give **17a** (as a major product) and **18** (as a minor product). The two products were separated by dissolving in methanol and then filtered off to give the soluble product 18 and the insoluble product **17a**.

18: Yellow crystals (methanol), m.p. 218–220 °C, yield 24.4% (0.4 g). IR: 3321 (NH), 1587 (C=N). MS, *m/z* (%): 421 (M, 33), 422 (26), 344.2 (32), 318 (100). UV-Vis: 270 nm (ε 37 037), 320 nm (ε 31 250). For $C_{26}H_{20}FN_5$ (421.47) calculated: 74.09% C, 4.78% H, 16.62% N; found: 74.12% C, 4.76% H, 16.66% N.

N-(3-Amino-7-(4-fluorophenyl)-5-*p*-tolyl-3*H*-pyrrolo[2,3-*d*]pyrimidin-4(7*H*)-ylidene)-4-arylsulfonamide **19a** and **19b**. General Method

A mixture of **15** (0.01 mol) and benzene sulfonylchloride or toluene sulfonylchloride (0.012 mol) in benzene was stirred at room temperature for 1 h then left overnight at room temperature. The reaction mixture was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated under vacuum. The obtained solid product was crystallized to give **19a** and **19b**.

N-(3-Amino-7-(4-fluorophenyl)-5-p-tolyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-ylidene)benzenesulfonamide (**19a**): Colorless crystals (methanol), m.p. 208–210 °C, yield 73%. IR: 3455, 3314, 3224 (NH_2), 1657 (C=N). ^{1}H NMR (270 MHz): 2.3 (s, 3 H, CH_3), 6.62 (s, 2 H, 2 NH), 7.3–7.98 (m, 13 H, ArH and C_6-H), 8.58 (s, 1 H, C_2-H). MS, *m/z* (%): 473 (M, 0.2), 334 (23), 333 (100). For $C_{25}H_{20}FN_5O_2S$ (473.52) calculated: 63.41% C, 4.26% H, 14.79% N, 6.77% S; found: 63.46% C, 4.32% H, 14.65% N, 6.82% S.

N-(3-Amino-7-(4-fluorophenyl)-5-p-tolyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-ylidene-4-methylbenzenesulfonamide (**19b**): Colorless crystals (methanol), m.p. 236–238 °C, yield 79.8%. IR: 3445, 3303, 3204 (NH_2), 1658 (C=N). ^{1}H NMR (270 MHz): 2.28 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 6.61 (b, 2 H, NH_2, D_2O-exchangeable), 7.09–7.98 (m, 13 H, ArH and CH-pyrrole), 8.58 (s, 1 H, C_2-H). MS, *m/z* (%): 487 (M^+, 0.40), 333 (100). For $C_{26}H_{22}FN_5O_2S$ (487.15) calculated: 64.05% C, 4.55% H, 14.36% N, 6.58% S; found: 64.12% C, 4.56% H, 14.42% N; 6.64% S.

7-(4-Fluorophenyl)-4-hydrazinyl-5-*p*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**20**)

A mixture of **11** (0.01 mol) and hydrazine hydrate (0.012 mol) in absolute ethanol (20 ml) was heated under reflux for 4h and then left to cool. The obtained solid product was filtered and crystallized to give **20** as colorless crystals (aqueous ethanol), m.p. 144–146 °C, yield 93.75% (1.5 g). IR: 3432, 3322 (NH, NH_2), 1579 (C=N), 1540 (C=C). MS, *m/z* (%): 333 (M, 100), 334 (23), 303 (56), 57 (42). ^{1}H NMR (270 MHz): 2.4 (s, 3 H, CH_3), 4.55 (s, 2 H, N-NH_2), 6.56 (b, 1 H, NH, D_2O-exchangeable), 7.36–7.93 (m, 9 H, ArH and CH-pyrrole), 8.37 (s, 1 H, C_2-H). For $C_{19}H_{16}FN_5$ (333.36) calculated: 68.46% C, 4.84% H, 21.01% N; found: 68.50% C, 4.90% H, 20.97% N.

7-(4-Fluorophenyl)-9-*p*-tolyl-7*H*-pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (**21**)

Method A. A mixture of sodium azide (0.072 g, 0.011 mol) and ammonium chloride (0.059 g, 0.011 mol) in DMSO (20 ml) was stirred for at 90 °C 5 min and the 4-chloro **11** (3.4 g, 0.01 mol) was added portion-wise while stirring. After complete addition, the reaction mixture was stirred for further 2.0–2.5 h at the same temperature and for 1 h at room temperature, then poured on crushed ice while stirring. The obtained solid product was filtered, washed with water, dried and crystallized from benzene–ethanol (2:1 v/v) to give the tetrazole **21**.

Method B. An aqueous solution of sodium nitrite (4.2 ml, 20% w/v) was slowly added portion-wise at ~0–5 °C to a stirred mixture of the hydrazine **20** (3.3 g, 0.01 mol) dissolved in acetic acid (40 ml). The reaction mixture was stirred for 2 h at the same temperature and then diluted with cold water. The obtained solid product was filtered, washed with aqueous sodium bicarbonate solution (20% w/v), followed by another water washing, dried and crystallized to give the tetrazole **21** (m.p. and mixed m.p. no depression with the sample ob-

tained from method *A*) as colorless crystals (benzene–ethanol 2:1 v/v), m.p. 224–226 °C, yield 90.63% (0.75 g) (method *A*) and 66% (0.64 g) (method *B*), respectively. IR: 1615 (C=N), 1512 (C=C). MS, *m/z* (%): 345 (7), 344 (M^+, 35), 316 (100). ^{1}H NMR (270 MHz): 2.3 (s, 3 H, CH_3), 7.24–8.39 (m, 9 H, ArH and CH-pyrrole), 9.88 (s, 1 H, C_2-H). For $C_{19}H_{13}FN_6$ (344.35) calculated: 66.27% C, 3.81% H, 24.41% N; found: 66.25% C, 3.83% H, 24.47% N.

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