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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Evaluation of the anti-inflammatory activity of some pyrrolo[*2,3-d*]pyrimidine derivatives

Mosaad S. Mohamed · Rehab Kamel · Rania H. Abd El-hameed

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Abstract A series of novel pyrrolo[*2,3-d*]pyrimidine and fused pyrrolo[*2,3-d*]pyrimidine derivatives were synthesized and their structures were characterized by elemental analysis, ^{1}H NMR, IR, and mass spectroscopy. Their in vivo anti-inflammatory activities were evaluated, and the results indicated that some of the title compounds compounds showed significant activities. These compounds are **2b** ((7-(4-Methoxyphenyl)-5,6-diphenyl-7H-pyrrolo[*2,3-d*]pyrimidin-4-yl)-hydrazine), **7b** (4-(2-(Benzyl)hydrazinyl)-7-(4-methoxyphenyl)-5,6-diphenyl-7H-pyrrolo[*2,3-d*] pyrimidine), **7d** (4-(2-(Benzyl)hydrazinyl)-7-(4-methoxyphenyl)-5-phenyl-7H-pyrrolo[*2,3-d*]pyrimidine), and **9b** (4-(3,5-Dimethyl-4H-pyrazol -1-yl)-7-(4-Methoxyphenyl)-5,6-diphenyl-4,7dihydro-3H-pyrrolo[*2,3-d*]pyrimidine).

Keywords Pyrrolo[*2,3-d*]pyrimidine · Pyrrolo[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine · Anti-inflammatory activity · Structure–activity relationship

Introduction

Inflammation is a normal protective response to tissue injury caused by several causes (Mycek *et al*., 1987). Inflammation is triggered by the release of chemical mediators from the injured tissue and migrating cells where prostaglandins play a very important role as mediators in the process of inflammation. Almost all classes of non-steroidal ant-inflammatory drugs (NSAIDs) inhibit the conversion of arachidonic acid to prostaglandins. The carrageenin-induced rat hind paw edema test is a common model for evaluation of anti-inflammatory agents; in this model, cyclooxygenase-2 (COX-2) levels are raised and this is accompanied with the increase in prostaglandin production (Huslisson, 1983; Evans and Nigel, 1987). Pyrrolo[*2,3-d*]pyrimidine derivatives have attracted a great deal of interest owing to their medicinal activities as they have wide variety of interesting biological activities such as anti-microbial (Rao, 1968; Dang and Gomez-Galeno, 2002), analgesic (Danchev *et al*., 2006), anti-inflammatory (Jarvis *et al*., 2002), antiviral (Gangjee *et al*., 2005), and anti-cancer (Declercq *et al*., 1987; Krawczyk *et al*., 1995; Finch *et al*., 1997). The rapid growth in the literature dealing with the synthesis and anti-inflammatory activity of the pyrrolo[*2,3-d*]pyrimidine derivatives prompted us to synthesize new derivatives of pyrrolo[*2,3-d*]pyrimidine and fused pyrrolopyrimidine derivatives and test their anti-inflammatory activity as an extension to our previous work (Mohamed *et al*., 2012).

Chemistry

Compounds **1a**–**1d** were prepared as we reported before (Mohamed *et al*., 2011). These compounds were utilized for the preparation of hydrazino-pyrrolo[*2,3-d*]pyrimidine derivatives **2a**–**2d** using hydrazine hydrate (Mohamed *et al*., 2005). These hydrazino derivatives were the key compounds for preparation of all the rest pyrrolopyrimidine derivatives. Pyrrolo[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine derivatives

M. S. Mohamed · R. H. Abd El-hameed (✉)
Pharmaceutical Organic Chemistry Department,
Faculty of Pharmacy, Helwan University,
Ein Helwan, Cairo, Egypt
e-mail: zeiadomar@yahoo.com

R. Kamel
Toxicology and Pharmacology Department,
Faculty of Pharmacy, Helwan University,
Ein Helwan, Cairo, Egypt

3–6 were synthesized via reaction of compounds **2a–2d** with formic acid, carbon disulfide, acetic anhydride, or ethyl chloroformate (Abdel-Mohsen, 2005; Hossain and Bhuiyan, 2009; Fathalla *et al*., 2009) as revealed in Scheme 1.

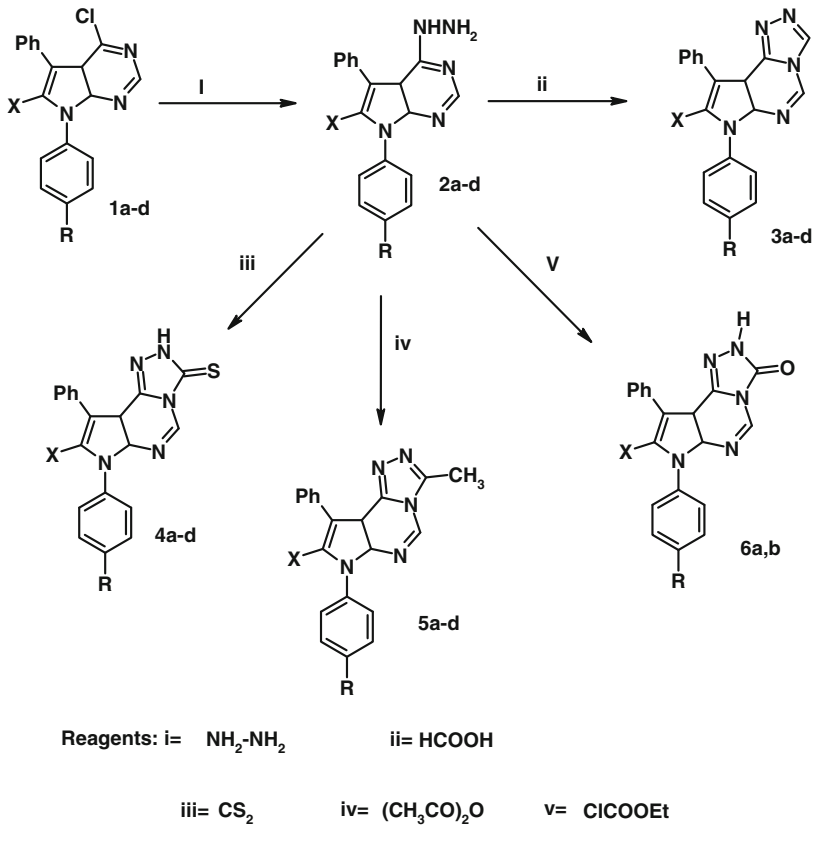
Refluxing of **2a–2d** with the benzaldehyde in absolute ethanol gave 4-(2-benzylhydrazinyl)pyrrolopyrimidine derivatives **7a–7d** (Hossain and Bhuiyan, 2009). Compounds **2a** and **2b** were cyclized to pyrrolo[3,2-*e*]tetrazolo[1,5-*c*] pyrimidine **8a** and **8b** by stirring with sodium nitrite in acetic acid (Dave and Shah, 2002). 4-Pyrazolyl-pyrrolo[*2,3-d*]pyrimidine **9b–9d** were prepared by refluxing of hydrazino-pyrrolopyrimidine **2b–2d** with acetyl acetone (Bhuiyan *et al*., 2005). Finally, pyrrolo[3,2-*e*][1,2,5]triazino[5,6-*c*]pyrimidin-3-one **10a** and **10b** were produced when compounds **2a** and **2b** were refluxed with chloro acetyl-chloride (Fathalla *et al*., 2009) as revealed in Scheme 2.

Biological activity

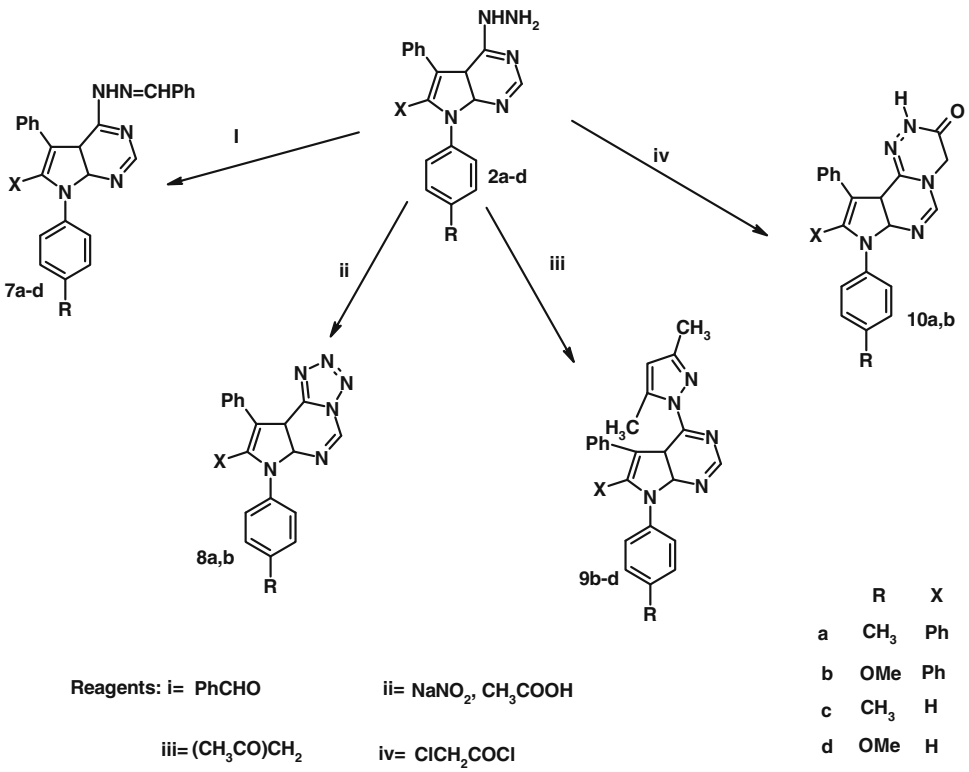
All the synthesized compounds were tested for their anti-inflammatory activity. As indicated in Table 1, compounds **2b**, **7b**, **7d**, and **9b** induced a good anti-inflammatory activity at both 3 and 4-h interval postcarrageenan, comparable with that of ibuprofen and their activity profiles were the same as ibuprofen (response increasing by time). Compound **9b** exerted a stronger anti-inflammatory effect than ibuprofen (63.24 and 74.6 % inhibition, respectively, at 3 and 4 h interval postcarrageenan). Likewise, compounds **2b and 7d** showed a significantly higher inhibitory action than ibuprofen at the 3 h interval (61.4 and 62.68 % inhibition, respectively) but their activity at 4 h interval postcarrageenan was lower than that of ibuprofen (62.38 and 66.19 %). Activity of compound **7b** was lower than that of ibuprofen at both 3 and 4 h interval postcarrageenan (54.04 and 62.96 % inhibition, respectively). Compounds **2d**, **9c**, and **9d** showed no significant anti-inflammatory activity at 1, 2, and 3 h interval but their significant activity only appeared at 4 h interval but less than that of ibuprofen (50.26, 59.25, and 61.9 % respectively). The rest of the tested compounds showed no activity.

In order to analyze structure–activity relationships, two structural components were considered: the nature of the heterocycle nucleus and the nature of the substituent on positions 4 and 7 of pyrrolo[*2,3-d*]pyrimidine. First, regarding the influence of the nature of the heterocycle nucleus, it is generally observed that pyrrolo[*2,3-d*]pyrimidine derivatives acquired significant anti-inflammatory activity as compounds **2b**, **2d**, **7b**, **7d**, and **9c–d** over pyrrolo[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine derivatives **3a–3d–6a–6d**, pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine **8a** and **8b**, and pyrrolo[3,2-*e*][1,2,5]triazino[5,6-*c*]pyrimidine **10a** and **10b** which have no

Scheme 1 Synthesis of compounds **2–6**



Scheme 2 Synthesis of compounds **7–10**



significant activity. Regarding the nature of the substituent, the four 4-chloro-pyrrolo[*2,3-d*]pyrimidine derivatives **1a–1d** showed no activity as anti-inflammatory agents; by converting them to 4-hydrazino-pyrrolopyrimidine derivatives **(2a–2d)**, two derivatives only showed anti-inflammatory activity which are **2b** and **2d** (both have 4-Methoxyphenyl group in position 7). Condensation of 4-hydrazino-pyrrolopyrimidines with benzaldehyde producing **7a–7d**, among them **7b** and **7d** retained the anti-inflammatory activity. 4-Pyrazolyl-pyrrolo[*2,3-d*]pyrimidine derivatives **9b–9**d have significant activity as anti-inflammatory agents (Table 1).

Summary

In the present study, we described a straightforward and efficient synthesis of novel pyrrolo[*2,3-d*]pyrimidine and fused pyrrolo[*2,3-d*]pyrimidine derivatives as anti-inflammatory agents. Some of the synthesized pyrrolo[*2,3-d*] pyrimidine compounds are promising anti-inflammatory agents, while pyrrolopyrimidine derivatives fused with third ring have no anti-inflammatory activity Fig. 1.

Experimental section

All melting points were uncorrected and measured using Electro-thermal IA 9100 apparatus (Shimadzu, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (USA), Faculty of Science, Cairo University, Cairo, Egypt. 1H NMR spectra were determined on a Varian Mercury (300 MHz) spectrometer (Varian UK) and chemical shifts were expressed as ppm against TMS as internal reference (Faculty of Science, Cairo University, Cairo, Egypt). Mass spectra were recorded on 70 eV EI Ms-QP 1000 EX (Shimadzu, Japan), Faculty of Science, Cairo University, Cairo, Egypt. Microanalyses were operated using Vario, Elmentar apparatus (Shimadzu, Japan), Organic Microanalysis Unit, Faculty of Science, Cairo University, Cairo, Egypt. Column Chromatography was performed on (Merck) Silica gel 60 (particle size 0.06–0.20 mm). Compounds **1a–1d** were prepared as reported in the literature (Mohamed *et al.*, 2011). All new compounds yielded spectral data consistent with the proposed structure and microanalysis within ±0.4 % of the theoretical values.

Anti-inflammatory activity

Animals

Young adult male Sprague–Dawley rats (5 rats per group), weighing 140–170 g, were housed at cages in a temperature-controlled (25 ± 1 °C) environment and provided free access to pelleted food and purified drinking water ad libitum. The animal experiments described below comply with the ethical

Table 1 In vivo anti-inflammatory activity

Compounds	Edema induced by carrageenan (% edema inhibition relative to control)							
	1 h		2 h		3 h		4 h	
	Infl ± SE	% inh	Infl ± SE	% inh	Infl ± SE	% inh	Infl ± SE	% inh
1a	0.221 ± 0.041	3.92	0.234 ± 0.043	10	0.373 ± 0.013	31.43	0.452 ± 0.083	28.59
1b	0.401 ± 0.034	0	0.398 ± 0.072	0	0.361 ± 0.078	33.64	0.344 ± 0.027	45.39
1c	0.227 ± 0.023	1.3	0.255 ± 0.083	1.92	0.374 ± 0.063	31.25	0.515 ± 0.061	18.25
1d	0.199 ± 0.067	13.4	0.215 ± 0.075	17.3	0.365 ± 0.042	32.9	0.511 ± 0.012	18.89
2a	0.247 ± 0.086	0	0.34 ± 0.034	0	0.383 ± 0.017	29.6	0.513 ± 0.043	18.57
2b	0.199 ± 0.051	13.48	0.216 ± 0.042	16.92	0.21 ± 0.017**	61.4	0.237 ± 0.043**	62.38
2c	0.28 ± 0.069	0	0.373 ± 0.013	0	0.297 ± 0.054	45.4	0.383 ± 0.052	39.21
2d	0.177 ± 0.027	23.04	0.237 ± 0.062	8.85	0.317 ± 0.034	41.73	0.313 ± 0.087*	50.26
3a	0.36 ± 0.042	0	0.365 ± 0.037	0	0.462 ± 0.073	15.07	0.35 ± 0.029	44.44
3b	0.21 ± 0.053	8.69	0.219 ± 0.057	15.77	0.392 ± 0.026	27.94	0.33 ± 0.025	47.62
3c	0.426 ± 0.052	0	0.401 ± 0.067	0	0.487 ± 0.073	10.48	0.45 ± 0.009	28.57
3d	0.456 ± 0.039	0	0.415 ± 0.064	0	0.362 ± 0.018	33.46	0.402 ± 0.025	36.19
4a	0.54 ± 0.026	0	0.233 ± 0.0227	10.38	0.45 ± 0.075	17.27	0.48 ± 0.021	23.81
4b	0.213 ± 0.059	7.39	0.207 ± 0.0109	20.38	0.438 ± 0.014	19.49	0.412 ± 0.04	34.6
4c	0.223 ± 0.076	3.04	0.21 ± 0.017	19.23	0.36 ± 0.048	33.8	0.383 ± 0.035	39.21
4d	0.34 ± 0.014	0	0.352 ± 0.074	0	0.39 ± 0.029	28.31	0.33 ± 0.027	47.62
5a	0.213 ± 0.008	7.39	0.234 ± 0.083	10	0.452 ± 0.071	16.91	0.48 ± 0.084	23.81
5b	0.42 ± 0.009	0	0.406 ± 0.034	0	0.467 ± 0.072	14.15	0.452 ± 0.004	28.25
5c	0.203 ± 0.021	11.74	0.211 ± 0.027	18.85	0.383 ± 0.05	29.5	0.423 ± 0.017	32.85
5d	0.193 ± 0.049	15.94	0.217 ± 0.036	0.5416	0.397 ± 0.033	27.8	0.403 ± 0.048	35.98
6a	0.273 ± 0.028	0	0.3 ± 0.089	0	0.437 ± 0.065	19.7	0.36 ± 0.0101	42.85
6b	0.227 ± 0.0419	1.45	0.233 ± 0.078	10.38	0.44 ± 0.026	18.5	0.4 ± 0.031	36.5
7a	0.41 ± 0.078	0	0.44 ± 0.007	0	0.46 ± 0.081	15.44	0.423 ± 0.037	32.8
7b	0.19 ± 0.019	17.39	0.176 ± 0.071	32.31	0.25 ± 0.023**	54.04	0.233 ± 0.005**	62.96
7c	0.313 ± 0.034	0	0.296 ± 0.019	0	0.393 ± 0.012	27.7	0.367 ± 0.039	41.8
7d	0.177 ± 0.037	23.04	0.18 ± 0.022	30.77	0.203 ± 0.013**	62.68	0.213 ± 0.072**	66.19
8a	0.217 ± 0.027	5.65	0.23 ± 0.005	11.54	0.398 ± 0.010	26.83	0.431 ± 0.04	31.59
8b	0.54 ± 0.016	0	0.352 ± 0.071	0	0.437 ± 0.018	19.7	0.383 ± 0.002	39.21
9b	0.293 ± 0.037	0	0.243 ± 0.018	6.41	0.2 ± 0.006**	63.24	0.16 ± 0.044**	74.6
9c	0.21 ± 0.038	8.7	0.253 ± 0.014	2.56	0.373 ± 0.022	31.37	0.257 ± 0.075*	59.25
9d	0.212 ± 0.027	7.82	0.198 ± 0.017	23.85	0.35 ± 0.054	35.66	0.24 ± 0.033**	61.9
10a	0.19 ± 0.051	17.39	0.2 ± 0.037	23.08	0.39 ± 0.025	28.31	0.41 ± 0.086	34.92
10b	0.41 ± 0.028	0	0.34 ± 0.037	0	0.46 ± 0.082	15.44	0.423 ± 0.007	32.8
Ibuprofen	0.216 ± 0.034	6.08	0.1425 ± 0.031	45	0.214 ± 0.024	60.66	0192 ± 0.012	69.52
Control	0.23 ± 0.033		0.26 ± 0.049		0.544 ± 0.081		0.63 ± 0.037	

infl mean difference in rat paw volume between right and left paw. ±SE, *%inhibition* (1 − rt/rc) × 100 [*rt* infl. of tested group, *rc* infl. of control group], *Infl* inflammation, *SE* Standard Error, *%inh* % inhibition

Significantly different from ibuprofen as indicated: * $P < 0.01$; ** $P < 0.001$

principles and guidelines for the care and use of laboratory animals adopted by the National Egyptian Community.

Assessment of anti-inflammatory activity

Rat paw edema assay was carried out according to Winter *et al*. (Harrak *et al*., 2007).

Prepared compounds (equimolar to the reference drug) were dissolved in DMSO and administrated subcutaneously. One hour later, paw edema was induced by subplantar injection of 0.1 mL of 1 % carrageenan (Sigma-Aldrich, St. Louis, USA) into the right hind paw. Paw volume was measured using a water plethysmometer (Basile, Comerio, Italy). The difference between the right

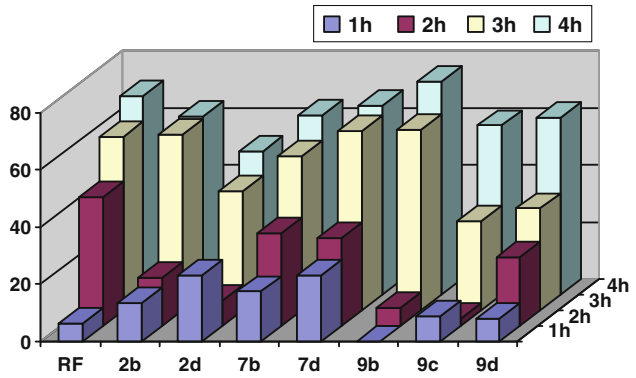


Fig. 1 Anti-inflammatory effect of active compound (% inhibition) compared to ibuprofen as reference drug

and left paw volume was measured at 1, 2, 3, and 4 h after induction of inflammation. Control group (five rats per group) received DMSO subcutaneously and carrageenan in subplantar region. Results were expressed as percentage inhibition of inflammation. Ibuprofen (70 mg/kg) was used as the reference drug (Winter *et al*., 1963).

Statistical analysis

Results are expressed as the mean ± SEM, and different groups were compared using one-way analysis of variance (ANOVA) followed by Tukey–Kramer test for multiple comparisons.

*Synthesis of (5-phenyl-6, 7-disubstituted-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-hydrazine (**2a–2d**)*

A mixture of 4-chloro pyrrolopyrimidine **1a–1d** (0.01 mol) and hydrazine hydrate (0.01 mol) was heated under reflux in absolute ethanol for 8 h, cooled, poured onto ice water to give precipitates which were filtered off, dried, and recrystallized from methanol to give compounds **2a–2d.**

*(7-(4-Methylphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-hydrazine **2a*** Yield: 82 %; m.p.: 204–206 °C; IR (KBr) υ (cm^{-1}): 3412, 3320 (NH_2), 3237 (N–H), 1533 (C=N); MS (EI) m/z: 391 (M^+, 34 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.46 (s, 3H, CH_3), 4.9 (br s, 2H, NH_2, D_2O exchangeable), 6.7–7.9 (m, 15H, Ar–H, NH, D_2O exchangeable), 8.3 (s, 1H, C2-H); Anal. Calcd for $C_{25}H_{21}N_5$ (391.48): C, 76.70; H, 5.41; N, 17.89 %. Found: C, 76.93; H, 5.12; N, 17.56 %.

*(7-(4-Methoxyphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-hydrazine **2b*** Yield: 91 %; m.p.: 224–226 °C; IR (KBr) υ (cm^{-1}): 3430, 3414 (NH_2), 3212 (N–H), 1612 (C=N), 1227 (C–O); MS (EI) m/z: 407 (M^+, 5.6 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.39 (s, 3H, OCH_3), 5.2 (br s, 2H, NH_2, D_2O exchangeable), 6.9–7.9 (m, 15H, Ar–H, NH, D_2O exchangeable), 8.21 (s, 1H, C2-H); Anal. Calcd for $C_{25}H_{21}N_5O$ (407.48): C, 73.69; H, 5.19; N, 17.19; O, 3.93 %. Found: C, 73.34; H, 4.96; N, 16.88; O, 4.08 %.

*(7-(4-Methylphenyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-hydrazine **2c*** Yield: 78 %; m.p.: 201–203 °C; IR (KBr) υ (cm^{-1}): 3427, 3385 (NH_2), 3217 (N–H), 1558 (C=N); MS (EI) m/z: 315 (M^+, 16.2 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.2 (s, 3H, CH_3), 5.18 (br s, 2H, NH_2, D_2O exchangeable), 7.0-8.0 (m, 11H, Ar–H, NH, D_2O exchangeable), 8.34 (s, 1H, C2-H); Anal. Calcd for $C_{19}H_{17}N_5$ (315.38): C, 72.36; H, 5.43; N, 22.21 %. Found: C, 72.51; H, 5.55; N, 21.94 %.

*(7-(4-Methoxyphenyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-hydrazine **2d*** Yield: 83 %; m.p.: 209–211 °C; IR (KBr) υ (cm^{-1}): 3378, 3312 (NH_2), 3167 (N–H), 1603 (C=N), 1233 (C–O); MS (EI) m/z: 331 (M^+, 14.7 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.42 (s, 3H, OCH_3), 4.78 (br s, 2H, NH_2, D_2O exchangeable), 6.8–7.7 (m, 11H, Ar–H, NH, D_2O exchangeable), 8.05 (s, 1H, C2-H); Anal. Calcd for $C_{19}H_{17}N_5O$ (331.38): C, 68.87; H, 5.17; N, 21.13; O, 4.83 %. Found: C, 69.15; H, 5.36; N, 20.86; O, 4.55 %.

*Synthesis of 9-phenyl-7,8-disubstituted-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (**3a–3d**)*

The appropriate hydrazine **2a–2d** (0.01 mol) was heated under reflux for 8 h in formic acid (20 ml, 85 %), cooled, poured onto ice water to give a precipitate which was filtered off, dried, and recrystallized from ethanol to yield compounds **3a–3d**.

*7-(4-Methylphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine **3a*** Yield: 64 %; m.p.: 176–178 °C; IR (KBr) υ (cm^{-1}): 1613 (C=N); MS (EI) m/z: 401 (M^+, 100 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.34 (s, 3H, CH_3), 6.94–7.96 (m, 14H, Ar–H), 8.0 (s, 1H, C3-H), 8.9 (s, 1H, C5-H); Anal. Calcd for $C_{26}H_{19}N_5$ (401.47): C, 77.79; H, 4.77; N, 17.44 %. Found: C, 78.03; H, 5.02; N, 17.81 %.

*7-(4-Methoxyphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine **3b*** Yield: 73 %; m.p.: 192–194 °C; IR (KBr) υ (cm^{-1}): 1598 (C=N), 1224 (C–O); MS (EI) m/z: 417 (M^+, 57 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.64 (s, 3H, OCH_3), 6.8–7.4 (m, 14H, Ar–H), 7.91 (s, 1H, C3-H), 8.3 (s, 1H, C5-H); Anal. Calcd for $C_{26}H_{19}N_5O$ (417.47): C, 74.80; H, 4.59; N, 16.78; O, 3.83 %. Found: C, 75.04; H, 4.91; N, 16.36; O, 3.66 %.

7-(4-Methylphenyl)-9-phenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine ***3c*** Yield: 79 %; m.p.: 188–190 °C; IR (KBr) υ (cm^{-1}): 1609 (C=N); MS (EI) m/z: 325 (M^+, 43.6 %), ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.25 (s, 3H, CH_3), 6.9–7.8 (m, 10H, Ar–H), 8.11 (s, 1H, C3-H), 8.47 (s, 1H, C5-H); Anal. Calcd for $C_{20}H_{15}N_5$ (325.38): C, 73.83; H, 4.65; N, 21.25 %. Found: C, 74.05; H, 4.59; N, 21.56 %.

7-(4-Methoxyphenyl)-9-phenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine ***3d*** Yield: 82 %; m.p.: 187–189 °C; IR (KBr) υ (cm^{-1}): 1573 (C=N), 1218 (C–O); MS (EI) m/z: 341 (M^+, 12.8 %), ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.49 (s, 3H, OCH_3), 7.0–7.9 (m, 10H, Ar–H), 8.13 (s, 1H, C3-H), 8.4 (s, 1H, C5-H); Anal. Calcd for $C_{20}H_{15}N_5O$ (341.38): C, 70.37; H, 4.43; N, 20.52; O, 4.69 %. Found: C, 69.95; H, 4.17; N, 20.86; O, 4.34 %.

*Synthesis of 9-phenyl-7,8-disubstituted-7H-pyrrolo [3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-3-thione (**4a–4d**)*

A mixture of the appropriate hydrazine **2a–2d** (0.01 mol) and carbon disulfide (0.01 mol) was heated under reflux for 3 h in absolute ethanol (30 ml), cooled, poured onto ice water to give a precipitate which was filtered off, dried, and recrystallized from ethanol to yield compounds **4a–4d**.

7-(4-Methylphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e][1,2,4] triazolo[4,3-c]pyramid in-3-thione ***4a*** Yield: 52 %; m.p.: 190–192 °C; IR (KBr) υ (cm^{-1}): 3314 (N–H), 1652 (C=S), 1567 (C=N); MS (EI) m/z: 433 (M^+, 13 %), ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.36 (s, 3H, CH_3), 6.8–7.5 (m, 14H, Ar–H), 8.89 (s, 1H, C5-H), 8.98 (br s,1H, NH, D_2O exchangeable); Anal. Calcd for $C_{26}H_{19}N_5S$ (433.54): C, 72.03; H, 4.42; N, 16.15; S, 7.40 %. Found: C, 71.85; H, 4.78; N, 15.83; S, 7.14 %.

7-(4-Methoxyphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e][1,2,4] triazolo[4,3-c]pyrimid in-3-thione ***4b*** Yield: 63 %; m.p.: 209–211 °C; IR (KBr) υ (cm^{-1}): 3278 (N–H), 1649 (C=S), 1598 (C=N), 1253 (C–O); MS (EI) m/z: 449 (M^+, 8.5 %), ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.6(s, 3H, OCH_3), 6.8–8.0 (m, 14H, Ar–H), 8.2(s, 1H, C5-H), 8.4 (s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{26}H_{19}N_5OS$ (449.54): C, 69.47; H, 4.26; N, 15.58; O, 3.56; S, 7.13 %. Found: C, 69.13; H, 4.52; N, 15.27; O, 3.84; S, 6.82 %.

7-(4-Methylphenyl)-9-phenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-3-thione ***4c*** Yield: 68 %; m.p.: 185–187 °C; IR (KBr) υ (cm^{-1}): 3301 (N–H), 1658(C=S), 1602 (C=N); MS (EI) m/z: 357 (M^+, 17 %), ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.6(s, 3H, CH_3), 6.8–7.7 (m, 10H, Ar–H), 8.1(s, 1H, C5-H), 8.29(s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{20}H_{15}N_5S$ (357.44): C, 67.21; H, 4.23; N, 19.59; S, 8.97 %. Found: C, 67.48; H, 4.57; N, 19.23; S, 9.13 %.

7-(4-Methoxyphenyl)-9-phenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-3-thione ***4d*** Yield: 64 %; m.p.: 179–181 °C; IR (KBr) υ (cm^{-1}): 3325 (N–H), 1663 (C=S), 1618 (C=N), 1248 (C–O); MS (EI) m/z: 373 (M^+, 23.6 %), ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.43(s, 3H, OCH_3), 6.9–7.9 (m, 10H, Ar–H), 8.32(s, 1H, C5-H), 8.5 (s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{20}H_{15}N_5OS$ (373.44): C, 64.33; H, 4.05; N, 18.75; O, 4.28; S, 8.59 %. Found: C, 64.71; H, 4.37; N, 19.02; O, 4.54; S, 8.47 %.

*Synthesis of 3-methyl-9-phenyl-7,8-disubstituted-7H-pyrrolo[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine (**5a–5d**)*

The appropriate hydrazine **2a–2d** (0.01 mol) was heated under reflux for 5 h in acetic anhydride (30 ml), cooled, poured onto ice water and neutralize with ammonia to give a precipitate which was filtered off, dried, and recrystallized from ethanol to yield compounds **5a–5d**.

3-Methyl-7-(4-methylphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine ***5a*** Yield: 59 %; m.p.: 185–187 °C; IR (KBr) υ (cm^{-1}): 1598 (C=N); MS (EI) m/z: 415 (M^+, 6.49 %), ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.21 (s, 3H, C3-CH_3), 2.32 (s, 3H, Ar-CH_3), 6.98–7.6 (m, 14H, Ar–H), 8.2 (s, 1H, C5-H); Anal. Calcd for $C_{27}H_{21}N_5$ (415.50): C, 78.05; H, 5.09; N, 16.86 %. Found: C, 78.35; H, 5.24; N, 17.03 %.

3-Methyl-7-(4-methoxyphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine ***5b*** Yield: 47 %; m.p.: 199–201 °C; IR (KBr) υ (cm^{-1}): 1614 (C=N), 1243 (C–O); MS (EI) m/z: 431 (M^+, 22 %), ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.04 (s, 3H, C3-CH_3), 3.7 (s, 3H, OCH_3), 6.8–7.9, m, 14H, Ar–H), 8.15 (s, 1H, C5-H); Anal. Calcd for $C_{27}H_{21}N_5O$ (431.50): C, 75.16; H, 4.91; N, 16.23; O, 3.71 %. Found: C, 75.01; H, 5.11; N, 16.39; O, 3.99 %.

3-Methyl-7-(4-Methylphenyl)-9-phenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine ***5c*** Yield: 52 %; m.p.: 181–183 °C; IR (KBr) υ (cm^{-1}): 1620 (C=N); MS (EI) m/z: 339 (M^+, 46 %), ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.2 (s, 3H, C3-CH_3), 2.29(s, 3H, CH_3), 6.8–7.8, m, 10H, Ar–H), 8.03(s, 1H, C5-H); Anal. Calcd for $C_{21}H_{17}N_5$ (339.40): C, 74.32; H, 5.05; N, 20.63 %. Found: C, 74.65; H, 5.42; N, 21.02 %.

3-Methyl-7-(4-methoxyphenyl)-9-phenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine ***5d*** Yield: 66 %;

m.p.: 194–196 °C; IR (KBr) υ (cm^{-1}): 1583 (C=N), 1222 (C–O); MS (EI) m/z: 355 (M^+, 19.8 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.3 (s, 3H, C3-CH_3), 3.68 (s, 3H, OCH_3), 7.0–7.9, m, 10H, Ar–H), 8.21 (s, 1H, C5-H); Anal. Calcd for $C_{21}H_{17}N_5O$ (355.40): C, 70.97; H, 4.82; N, 19.71; O, 4.50 %. Found: C, 71.16; H, 4.53; N, 20.05; O, 4.39 %.

*Synthesis of 9-phenyl-7,8-disubstituted-7H-pyrrolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-3-one (**6a, 6b**)*

A solution of the appropriate hydrazine **2a**, **2b** (0.01 mol) in pyridine (10 ml) was cooled in ice bath and equimolar amount (0.01 mol) of ethyl chloroformate was added portion wise. Then the mixture was heated under reflux for 3 h, cooled, poured onto ice water and neutralize with HCl to give a precipitate which was filtered off, dried, and recrystallized from ethanol to yield compounds **6a**, **6b**.

*7-(4-Methylphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e][1,2,4] triazolo[4,3-c]pyrimid in-3-one **6a*** Yield: 54 %; m.p.: 226–228 °C; IR (KBr) υ (cm^{-1}): 3402 (N–H), 1624 (C=O), 1512 (C=N); MS (EI) m/z: 417 (M^+, 2.8 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.28(s, 3H, CH_3), 6.8–7.89 (m, 14H, Ar–H), 8.2(s, 1H, C5-H), 8.53(s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{26}H_{19}N_5O$ (417.47): C, 74.80; H, 4.59; N, 16.78 %. Found: C, 74.61; H, 4.35; N, 16.85 %.

*7-(4-Methoxyphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e][1,2,4] triazolo[4,3-c]pyrimid in-3-one **6b*** Yield: 60 %; m.p.: 239–241 °C; IR (KBr) υ (cm^{-1}): 3394(N–H), 1657 (C=O), 1602 (C=N), 1231 (C–O); MS (EI) m/z: 433 (M^+, 17 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.54(s, 3H, OCH_3), 6.8–8.0 (m, 14H, Ar–H), 8.31(s, 1H, C5-H), 8.54(s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{26}H_{19}N_5O_2$ (433.47): C, 72.04; H, 4.42; N, 16.16; O, 7.38 %. Found: C, 71.85; H, 4.74; N, 16.42; O, 7.69 %.

*Synthesis of 4-(2-(Benzyl)hydrazinyl)-5-phenyl-6, 7-disubstituted-7H-pyrrolo[2,3-d]pyrimidine(**7a–7d**)*

A mixture of the appropriate hydrazine **2a–2d** (0.01 mol) and benzaldehyde (0.01 mol) was heated under reflux in absolute ethanol for 8 h, cooled, poured onto ice water to give precipitates which were filtered off, dried, and recrystallized from methanol to give compounds **7a–7d**.

*4-(2-(Benzyl)hydrazinyl)-7-(4-methylphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidine **7a*** Yield: 32 %; m.p.: 187–189 °C; IR (KBr) υ (cm^{-1}): 3323(N–H), 1608 (C=N); MS (EI) m/z: 479 (M^+, 37.9 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.54(s, 3H, CH_3), 5.12(s, 1H, NH, D_2O exchangeable), 7.0–7.9 (m, 19H, Ar–H), 8.26(s, 1H, C2-H), 8.32(s, 1H, CH).; Anal. Calcd for $C_{32}H_{25}N_5$ (479.59): C, 80.14; H, 5.25; N, 14.60 %. Found: C, 79.82; H, 5.61; N, 14.36 %.

*4-(2-(Benzyl)hydrazinyl)-7-(4-methoxyphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidine **7b*** Yield: 45 %; m.p.: 239–241 °C; IR (KBr) υ (cm^{-1}): 3338(N–H), 1591 (C=N), 1213 (C–O); MS (EI) m/z: 495 (M^+, 7.3 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.5(s, 3H, OCH3), 4.5(s, 1H, NH, D_2O exchangeable), 6.7–7.8 (m, 19H, Ar–H), 8.0(s, 1H, C2-H), 8.2(s, 1H, CH); Anal. Calcd for $C_{32}H_{25}N_5O$ (495.59): C, 77.57; H, 5.05; N, 14.14; O, 3.23 %. Found: C, 77.79; H, 4.81; N, 14.47; O, 3.51 %.

*4-(2-(Benzyl)hydrazinyl)-7-(4-methylphenyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine **7c*** Yield: 39 %; m.p.: 224–226 °C; IR (KBr) υ (cm^{-1}): 3315(N–H), 1569 (C=N); MS (EI) m/z: 403 (M^+, 24 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.35(s, 3H, CH3), 4.85 (s, 1H, NH, D_2O exchangeable), 6.8–7.9 (m, 15H, Ar–H), 8.1(s, 1H, C2-H), 8.36(s, 1H, CH).; Anal. Calcd for $C_{26}H_{21}N_5$ (403.49): C, 77.40; H, 5.25; N, 17.36 %. Found: C, 77.73; H, 5.61; N, 17.02 %.

*4-(2-(Benzyl)hydrazinyl)-7-(4-methoxyphenyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidine **7d*** Yield: 41 %; m.p.: 175–177 °C; IR (KBr) υ (cm^{-1}): 3352(N–H), 1623 (C=N), 1236 (C–O); MS (EI) m/z: 419 (M^+, 12 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.62(s, 3H, OCH3), 5.2 (s, 1H, NH, D_2O exchangeable), 7.0–7.9 (m, 15H, Ar–H), 8.2(s, 1H, C2-H), 8.4(s, 1H, CH); Anal. Calcd for $C_{26}H_{21}N_5O$ (419.49): C, 74.46; H, 5.01; N, 16.71; O, 3.82 %. Found: C, 74.12; H, 4.77; N, 16.98; O, 3.98 %.

*Synthesis of 9-phenyl-7, 8-disubstituted-7H-pyrrolo[3, 2-e]tetrazolo[1,5-c]pyrimidine (**8a, 8b**)*

A mixture of the appropriate hydrazine **2a**, **2b** (0.01 mol) and sodium nitrite (0.69 gm, 0.01 mol dissolved in 5 ml H_2O) was stirred in glacial acetic acid (20 mL) at 40 °C for 8 h. The reaction mixture was poured onto ice water to give precipitates which were filtered, dried, and recrystallized from ethanol to yield compounds **8a**, **8b**.

*7-(4-Methylphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine **8a*** Yield: 37 %; m.p.: 219–221 °C; IR (KBr) υ (cm^{-1}): 3312 (N–H), 1623 (C=N); MS (EI) m/z: 402 (M^+, 26.9 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.36(s, 3H, CH_3), 6.7–7.9 (m, 14H, Ar–H), 8.2(s, 1H, C5-H); Anal. Calcd for $C_{25}H_{18}N_6$ (402.46): C, 74.61; H, 4.51; N, 20.88 %. Found: C, 74.99; H, 4.25; N, 20.54 %.

*7-(4-Methoxyphenyl)-8,9-diphenyl-7H-pyrrolo[3,2-e]tetrazolo[1,5-c]pyrimidine **8b*** Yield: 42 %; m.p.: 236–238 °C; IR (KBr) υ (cm^{-1}): 3279 (N–H), 1598 (C=N), 1253 (C–O); MS (EI) m/z: 418 (M^+, 19.5 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.62(s, 3H, OCH_3), 6.8–8.0 (m, 14H, Ar–H), 8.36(s, 1H, C5-H); Anal. Calcd for $C_{25}H_{18}N_6O$ (418.46): C, 71.76; H, 4.34; N, 20.08 %. Found: C, 71.52; H, 4.73; N, 19.86 %.

*Synthesis of 4-(3,5-dimethyl-4H-pyrazol-1-yl)-5-phenyl-6,7-disubstituted-4,7dihydro-3H-pyrrolo [2,3-d] pyrimidine (**9b–9d**)*

A Mixture of the appropriate hydrazine **2b–2d** (0.01 mol) and acetyl acetone (0.01 mol) in absolute ethanol was heated under reflux for 3 h, cooled, poured onto ice water to give a precipitate which was filtered off, dried, and recrystallized from ethanol to yield compounds **9b–9d**.

*4-(3,5-Dimethyl-4H-pyrazol-1-yl)-7-(4-methoxyphenyl)-5,6-diphenyl-4,7dihydro-3H-pyrrolo[2,3-d]pyrimidine (**9b**)* Yield: 38 %; m.p.: 196–198 °C; IR (KBr) υ (cm^{-1}): 1608 (C=N), 1231 (C–O); MS (EI) m/z: 471 (M^+, 5.57 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.2(s, 3H, CH_3), 2.32(s, 3H, CH_3), 3.4(s, 3H, OCH_3), 6.7 (s, 1H, pyrazole), 6.9–7.8 (m, 14H, Ar–H), 8.3(s, 1H, C2-H); Anal. Calcd for $C_{30}H_{25}N_5O$ (471.57): C, 76.41; H, 5.34; N, 14.85; O, 3.39 %. Found: C, 76.20; H, 5.67; N, 15.15; O, 3.67 %.

*4-(3,5-Dimethyl-4H-pyrazol-1-yl)-7-(4-methylphenyl)-5-phenyl-4,7dihydro-3H-pyrrolo[2,3-d]pyrimidine (**9c**)* Yield: 31 %; m.p.: 179–181 °C; IR (KBr) υ (cm^{-1}): 1583 (C=N), MS (EI) m/z: 379 (M^+, 13.8 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.2(s, 3H, CH_3), 2.34(s, 3H, CH_3), 2.47(s, 3H, CH_3), 6.73 (s, 1H, pyrazole), 6.97–7.9 (m, 10H, Ar–H), 8.2(s, 1H, C2-H); Anal. Calcd for $C_{24}H_{21}N_5$ (379.57): C, 75.99; H, 5.54; N, 18.47 %. Found: C, 76.24; H, 5.77; N, 18.38 %.

*4-(3,5-Dimethyl-4H-pyrazol-1-yl)-7-(4-methoxyphenyl)-5-phenyl-4,7dihydro-3H-pyrrolo[2,3-d]pyrimidine (**9d**)* Yield: 37 %; m.p.: 188–190 °C; IR (KBr) υ (cm^{-1}): 1602 (C=N), 1227 (C–O); MS (EI) m/z: 395 (M^+, 26 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.23(s, 3H, CH_3), 2.4(s, 3H, CH_3), 3.51(s, 3H, OCH_3), 6.8 (s, 1H, pyrazole), 7.0–7.9 (m, 10H, Ar–H), 8.32(s, 1H, C2-H); Anal. Calcd for $C_{24}H_{21}N_5O$ (395.57): C, 72.89; H, 5.35; N, 17.71; O, 4.05 %. Found: C, 73.14; H, 5.11; N, 17.98; O, 3.89 %.

*Synthesis of 10-phenyl-8,9-disubstituted-8H-pyrrolo[3,2-e][1,2,5]triazino[5,6-c]pyrimidin-3-one (**10a, 10b**)*

A mixture of the appropriate hydrazine **2a**, **b** (0.01 mol) and chloro-acetyl chloride (0.01 mol) was refluxed in absolute ethanol (20 mL) for 8 h. The reaction mixture was cooled, poured onto ice water to give precipitates which were filtered, dried, and recrystallized from ethanol to yield compounds **10a** and **10b**.

*8-(4-Methylphenyl)-9,10-diphenyl-8H-pyrrolo[3,2-e][1,2,5]triazino[5,6-c]pyrimidin-3-one (**10a**)* Yield: 35 %; m.p.: 216–218 °C; IR (KBr) υ (cm^{-1}): 3394 (N–H), 1635 (C=O), 1512 (C=N); MS (EI) m/z: 431 (M^+, 10 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.2(s, 3H, CH_3), 2.6 (s, 2H, CH2-C=O), 6.8–7.9 (m, 14H, Ar–H), 8.13 (s, 1H, NH), 8.34(s, 1H, C6-H); Anal. Calcd for $C_{27}H_{21}N_5O$ (431.50): C, 75.16; H, 4.91; N, 16.23; O, 3.71 %. Found: C, 75.38; H, 5.22; N, 16.46; O, 3.95 %.

*8-(4-Methoxyphenyl)-9,10-diphenyl-8H-pyrrolo[3,2-e][1,2,5]triazino[5,6-c]pyrimidin-3-one (**10b**)* Yield: 42 %; m.p.: 241–243 °C; IR (KBr) υ (cm^{-1}): 3418 (N–H), 1659 (C=O), 1588 (C=N), 1213 (C–O); MS (EI) m/z: 447 (M^+, 24.3 %), ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.52 (s, 2H, CH2-C=O), 3.46(s, 3H, OCH_3), 6.8–7.85 (m, 14H, Ar–H), 8.06 (s, 1H, NH), 8.26(s, 1H, C6-H); Anal. Calcd for $C_{27}H_{21}N_5O_2$ (447.50): C, 72.47; H, 4.73; N, 15.65; O, 7.15 %. Found: C, 72.71; H, 5.03; N, 15.79; O, 6.93 %.

References

Abdel-Mohsen SA (2005) Synthesis, reactions and antimicrobial activity of 2-amino-4-(8-quinolinol-5-yl)-1-(p-tolyl)-pyrrole-3-carbonitrile Bull. Korean Chem Soc 26:719–728

Bhuiyan MMH, Rahman KhMM, Hossain MI, Naser MA, Shumi W (2005) Fused pyrimidines. Part III: synthesis and antimicrobial activity of some furopyrimidines and imidazopyrazolopyrimidine. J Appl Sci Res 1:218–222

Danchev N, Bijev A, Yaneva D, Vladimirova S et al (2006) Synthesis, acute toxicity, and analgesic activity of new derivatives of pyrrole Arch. Pharm Chem Life Sci 339:670–674

Dang Q, Gomez-Galeno JE (2002) An efficient synthesis of pyrrolo[*2,3-d*]pyrimidines via inverse electron demand Diels-Alder reactions of 2-amino-4-cyanopyrroles with 1,3,5-triazines. J Org Chem 67:8703–8705

Dave ChG, Shah RD (2002) Annellation of triazole and tetrazole systems onto pyrrolo[*2,3-d*]pyrimidines: synthesis of tetrazolo[1,5-*c*]-pyrrolo[3,2-e]-pyrimidines and triazolo[1,5-*c*]pyrrolo-[3,2-*e*]pyrimidines as potential antibacterial agents. Molecules 7:554–565

Declercq E, Balzarini J, Madej D, Hansske F et al (1987) Synthesis and biological properties of sugar-modified analogues of the nucleoside antibiotics tubercidin, toyocamycin, sangivamycin, and formycin. J Med Chem 30:481–486

Evans D, Nigel WR (1987) Clinical Pharmacology 9 chap. 7. In: Williamson WR (ed) Anti-inflammatory compounds, 1st edn. Marcel Decker Inc., New York

Fathalla OA, Zeid IF, Haiba ME, Soliman AM, Abd-Elmoez ShI, El-Serwy WS (2009) Synthesis, antibacterial and anticancer evaluation of some pyrimidine derivatives. World J Chem 4:127–132

Finch RA, Revankar GR, Chan PK (1997) Structural and functional relationships of toyocamycin on NPM-translocation. AntiCancer Drug Des 12:205–215

Gangjee A, Jain HD, Kisliuk RL (2005) Novel 2-amino-4-oxo-5-arylthio-substituted-pyrrolo[*2,3-d*]pyrimidines as nonclassical antifolate inhibitors of thymidylate synthase Bioorg. Med Chem Lett 15:2225–2230

Harrak Y, Rosell G, Daidone G (2007) Synthesis and biological activity of new anti-inflammatory compounds containing the 1, 4-benzodioxine and/or pyrrole system. Bioorg Med Chem 15: 4876–4890

Hossain MI, Bhuiyan MMH (2009) Synthesis and antimicrobial activities of some new thieno and furopyrimidine derivatives. J Sci Res 1:317–325

Huslisson EC (1983) Clinical pharmacology and therapeutics series, 3 Chap. 1. In: Huskisson EC (ed) Antirheumatic drugs. Praeger, New York

Jarvis MF, Yu H, Cox BF, Polakowski J (2002) Analgesic and anti-inflammatory effects of A-286501, a novel orally active adenosine kinase inhibitor. Pain 96:107–118

Krawczyk SH, Nassiri MR, Kucera LS, Kern ER (1995) Synthesis and antiproliferative and antiviral activity of 2′-deoxy-2′-fluoro-arabinofuranosyl analogs of the nucleoside antibiotics toyocamycin and sangivamycin. J Med Chem 38:4106–4411

Mohamed MS, Rashad AE, Zaki MEA, Fatahala SS (2005) Synthesis and antimicrobial screening of some fused heterocyclic pyrroles. Acta Pharm (Zagreb, Croatia) 55:237–249

Mohamed MS, Hussein WM, McGeary RP, Vella P, Schenk G, Abd El-hameed RH (2011) Synthesis and kinetic testing of new inhibitors for a metallo-β-lactamase from *Klebsiella pneumonia* and *Pseudomonas aeruginosa*. Eur J Med Chem 46:6075–6082

Mohamed MS, Mostafa AG, Abd El-hameed RH (2012) Evaluation of the anti-inflammatory activity of novel synthesized pyrrole, pyrrolopyrimidine and spiropyrrolopyrimidine derivatives. Pharmacophore 3(1):44–54

Mycek MJ, Harrey RA, Champe PC (1987) Pharmacology Lippincott's illustrated reviews, 2nd edn. Lippincott Williams and Wilkins, Philadelphia, pp 401–420

Rao KV (1968) Structure of sangivamycin. J Med Chem 11:939–941

Winter CA, Risley EA, Nuss GW (1963) Anti-inflammatory and antipyretic activities of indomethacin, 1-(p-chlorobenzoyl)5-methoxy-2-methylindole-3-acetic acid. J Pharmacol Exp Ther 141: 369–376