Khalid Mohammed Hassan Hilmy

Department of Chemistry, Faculty of Science, Munoufiya University, Shebin El-Koom, Egypt

Synthesis of New Pyrrolo[2, 3-b]pyridines as a Potent Inhibitor of Tumour Necrosis Factor Alpha

The MAP kinase p38 plays a key role in the biosynthesis of the inflammatory cytokines tumor necrosis factor α (TNF-α) and 1L-1β. Accordingly, new pyrrolo[2,3-]pyridine derivatives **5 a–d** were prepared from 2-amino-3-cyanopyrroles **3 a–d** via the intermediate propenylaminopyrroles **4 a–d**. Then the compounds **5 a–d** were tested for their ability to inhibit the production of TNF-α *in vivo* in rats. The most potent compounds **5 a** and **5 b** possess enhanced ability to inhibit the production of TNF-α stimulated with bacterial lipopolysaccharide.

Keywords: Pyrrolo[2,3-b]pyridines; TNF-α inhibitor

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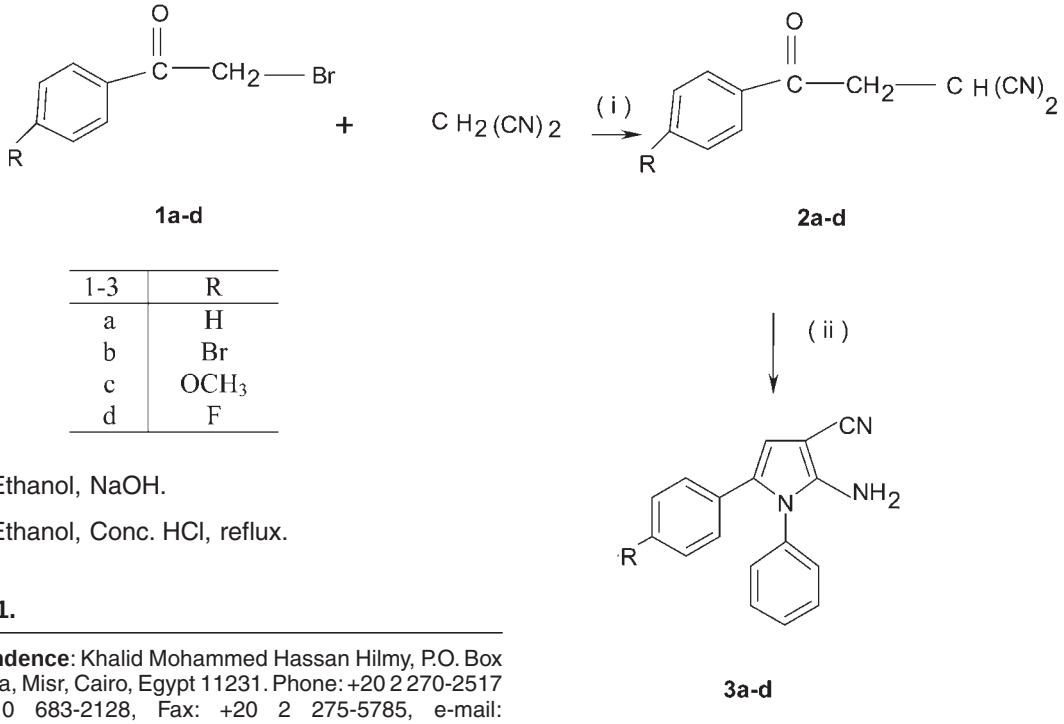
Introduction

Pyrrolo[2,3-b]pyridine derivatives deserve great interest because of their biological and physiological properties [1–6]. Tumor necrosis factor TNF-α and interleukin IL-1β are pro-inflammatory cyctokines and play an important role in inflammatory diseases such as rheumatoid arthritis (RA) [7–10], inflammatory bowel disease (IBD) [11], psoriasis [12], and Crohn's disease [13]. The release of and responses to, TNF-α and 1L-1β are regulated by a mitogen-activated protein (MAP) kinase, known as p38 [14–19]. Indeed, inhibitors of this kinase potently suppress the release of these pro-inflammatory cytokines from mononuclear phagocytes and block their actions in a variety of inflammatory cells. This paper reports the synthesis of some new pyrrolo[2,3-b]pyridines, which were tested for their ability to inhibit the production of TNF-α stimulated with bacterial lipopolysaccharide (LPS).

Results and discussion

The reaction of phenacylmalononitrile derivatives **2 a–d** with aniline under reflux in absolute ethanol in the pres-



1-3	R
a	H
b	Br
c	OCH_3
d	F

(i) Abs. Ethanol, NaOH.

(ii) Abs. Ethanol, Conc. HCl, reflux.

Scheme 1.

Correspondence: Khalid Mohammed Hassan Hilmy, P.O. Box 73, Shoubra, Misr, Cairo, Egypt 11231. Phone: +20 2 270-2517 or +20 10 683-2128, Fax: +20 2 275-5785, e-mail: khaledhilmy@hotmail.com

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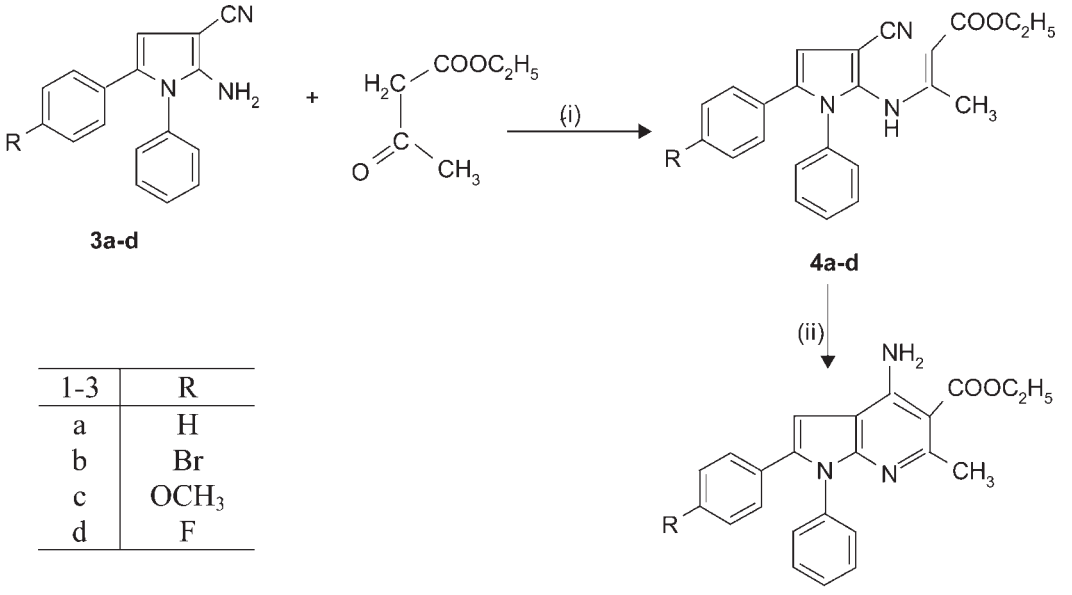

1-3	R
a	H
b	Br
c	OCH_3
d	F

(i) Dry tolune, p-TSO_3H, reflux, 2 h

(ii) Abs. Ethanol, Na, reflux, 3 h

Scheme 2.

ence of catalytic amounts of conc. HCl afforded a single product in each reaction; these compounds were identified as 1,5-disubtituted 2-amino-3-cyano-pyrroles **3a–d** (Scheme 1)**.** When **3a–d** were refluxed with ethyl acetoacetate in dry toluene and p-TSO_3H as a catalyst the products yielded were identified as propenylaminopyrroles **4a–d** (Scheme 2). The structure of compounds **4a–d** were based on the elemental and spectral data. On the other hand, when compounds **4a–d** were refluxed with sodium ethoxide in absolute ethanol intermolecular cyclization took place to give compounds **5a–d** (Scheme 2).

Propenylaminopyrroles **4a–d** showed characteristic bands in their IR spectra at 1661–1654 cm^{-1} for ester carbonyl, 2225–2227 cm^{-1} (CN), and at 3436–2970 cm^{-1} (NH) which confirmed their structures. The aromatic protons were resonated at δ 6.70–7.50 producing a multiplet together with a broad singlet at δ 9.90–9.97 (1 H) due to NH proton, and a broad singlet at δ 4.57–5.70 (2 H) for the NH_2 protons in the corresponding compounds **3a–d** in the ^{1}H-NMR ($CDCl_3$-d_6) spectra of **4a–d** disappeared**.** The structures of compounds **5a–d,** confirmed by the IR spectra exhibited vibrations near 3427–3458 cm^{-1} (NH_2) and 1669–1672 cm^{-1} (CO) for

Table 1. TNF-α inhibitation data of pyrrolo[2,3-b]pyridine derivatives **5a–d**.

Compound	Range ng/mL	Mean ng/mL	I. S. D	Value	Significance
Control	54–50	47.30	2.25		–
5a	4.5–5.2	4.80	0.35	<0.01	H.S
5b	0–3	0.13	0.15	<0.01	H.S
5c	70–77	73.00	3.60	>0.05	N.S
5d	30–70	50.00	20.00	>0.05	N.S

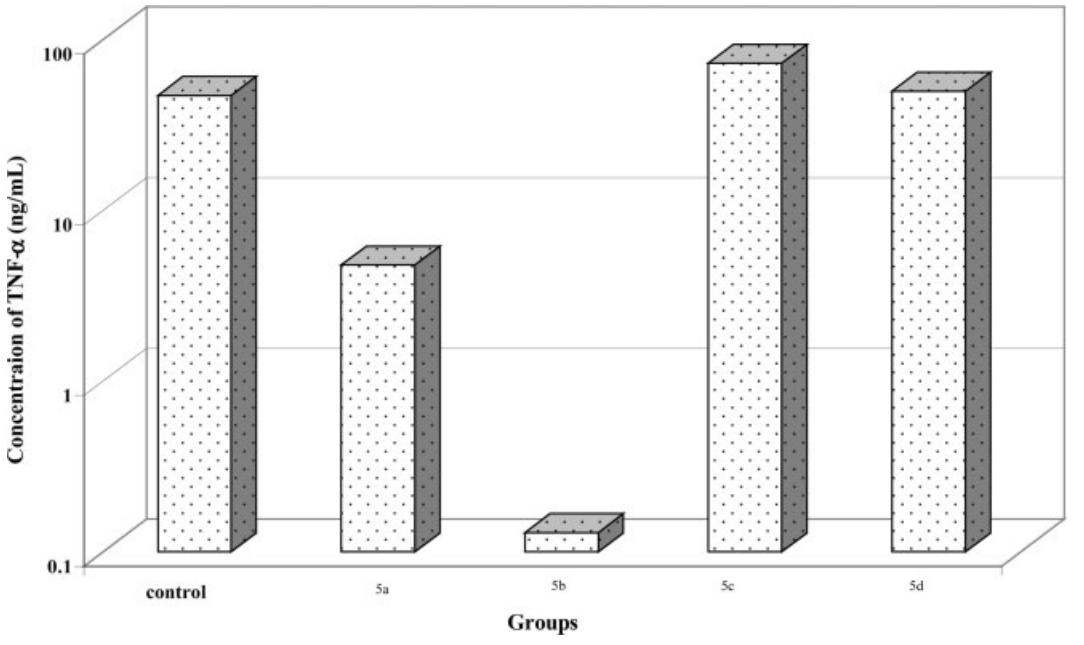

Figure 1. Effect of compounds **5 a–d** adminstrated on LPS (0.1 mg/kg) induced TNF-α release in male albino rats as a comparison.

ester carbonyl. A singlet at δ 6.85–6.95 (2 H) for (NH_2) and multiplet near δ 7.09–7.53 was found to be present because of aromatic protons in the ^{1}H-NMR (DMSO-d_6) spectra of compounds **5 a–d**. Compounds **5 a–d** were tested for their ability to inhibit the production of TNF-α (Table 1). The inhibitory effect of **5 a** and **5 b** may be due to the binding of these compounds at the active site of the transcription or translation processes of the TNF-α formation. In case of compound **5 c**, the methoxy group may form hydrogen bonding at any location far from the active site of the enzyme without any effect on the configuration and the activity of the active site, while compound **5 d** with the fluorine atom may attack the terminal NH_2 of the enzyme similar to Sangers reagent. This may be the reasons of inactivity of **5 c** and **5 d**. Figure 1 illustrates the effect of compunds **5 a–d** adminstrated on LPS (0.1 mg/kg) induced TNF-α release in male albino rats as a comparison.

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Experimental

Chemistry

Analytical data were recorded for the compounds described below using the following general procedures. IR spectra were recorded on KBr pellets on a Perkin Elmer 1720, Infrared Fourier Transform Spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for ^{1}H- and 75.5 MHz for ^{13}C-NMR with TMS as an internal standard. Chemical shifts were recorded in ppm (δ) from an internal tetramethylsilane standard in deuterochloroform or deuterodimethyl sulphoxide as specified below. EI spectra were recorded on a Finnigan MAT SSQ 710. All the above analytical data were recorded at the University of Southern Denmark. The progress of the reaction was monitored by TLC analytical silica gel plates 60 F_{254}. Merck silica gel (0.040–0.063 mm) was used for column chromatography (Merck, Darmstadt, Germany). Sovents were reagent grade and, when necessary, were purified and dried by standards methods. Sovents were removed under reduced pressure. Melting points were taken on an electro thermal melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA, USA.

General Procedure for the preparation of Phenacylmalononitriles **2 a–d**

To a stirred solution of equimolecular amounts (0.05 mol) of the substituted phenacyl bromides **1 a–d** and malononitrile (3.3 g) in ethanol (50 mL), a solution of sodium hydroxide (2 g, 0.05 mol) in water (50 mL) was added dropwise. After complete addition, the reaction mixture was diluted with water (50 mL) and the precipitate was collected and recrystallized from ethanol to give the phenacylmalononitrile derivatives **2 a–d,** respectively [20].

General Procedure for the preparation **3 a–d**

A mixture of aniline (0.01 mol) and 3-5 drops of conc. hydrochloric acid was added to a solution of phenacylmalononitrile derivatives **2 a–d** (0.01 mol) in ethanol (50 mL). This mixture

was refluxed for 5, 7, 9 days to obtain **3 a**, **3 b**, **3 c**, **d**, respectively and examined by TLC (Silica gel) with CH_2Cl_2/CH_3OH (39:1). The reaction mixture was then allowed to cool to room temperature. The precipitate was collected by filtration, dried, and recrystallized from ethanol. Synthesis of compound **3 a** has been reported previously [21].

2-Amino-5-(4-bromo-phenyl)-1-phenyl-1H-pyrrole-3-carbonitrile (**3 b**)

Yield (39 %), mp 200–201 °C; IR (cm^{-1}) (KBr): 3454, 3330, 3217 (NH_2), 2206 (CN); ^{1}H-NMR ($CDCl_3$-d_6): 4.57 (s, 2 H, NH_2), 6.52 (s, 1 H, 4-H), 6.90–7.70 (m, 9 H, $H_{arom.}$); ^{13}C-NMR ($CDCl_3$-d_6): 73.60 (C_3), 108.65 (C_4), 117.25 (CN), 120.56–135.58 (arom.), 147.53 (C_2); EI MS m/z 337 (M^+). Anal. Calcd. ($C_{17}H_{12}BrN_3$): C, 60.37; H, 3.58; N, 12.42. Found: C, 60.15; H, 3.70; N, 12.21.

2-Amino-5-(4-methoxy-phenyl)-1-phenyl-1H-pyrrole-3-carbonitrile (**3 c**)

Yield (53 %), mp 206–207 °C; IR (cm^{-1}) (KBr): 3377, 3250 (NH_2), 2203 (CN); ^{1}H-NMR (DMSO-d_6): 3.72 (s, 3 H, CH_3), 4.66 (s, 2 H, NH_2), 6.58 (s, 1 H, 4-H), 6.80–7.60 (m, 9 H, $H_{arom.}$); ^{13}C-NMR (DMSO-d_6): 55.05 (CH_3), 70.38 (C_3), 106.80 (C_4), 117.79 (CN), 123.80–138.82 (arom.), 145.31 (C_2); EI MS m/z 289 (M^+). Anal. Calcd. ($C_{18}H_{15}N_3O$. 0.25 H_2O): C, 73.51; H, 5.11; N,14.29. Found: C, 73.88; H, 5.27; N, 14.41.

2-Amino-5-(4-Fluoro-phenyl)-1-phenyl-1H-pyrrole-3-carbonitrile (**3 d**)

Yield (46 %); mp 169–170 °C; IR (cm^{-1}) (KBr): 3455, 3339, 3223 (NH_2), 2209 (CN); ^{1}H-NMR ($CDCl_3$-d_3): 4.62 (s, 2 H, NH_2), 6.57 (s, 1 H, 4-H), 6.80–7.70 (m, 9 H, $H_{arom.}$); ^{13}C-NMR ($CDCl_3$-d_6): 73.27 (C_3); 107.90 (C_4), 117.26 (CN), 127.98–135.50 (arom.), 146.72 (C_2); EI MS m/z 277 (M^+). Anal. Calcd. ($C_{17}H_{12}FN_3$): C, 73.63; H, 4.36; N,15.15. Found: C, 73.48; H, 4.46; N, 15.21.

General procedure for the preparation **4 a–d**

A mixture of **3 a–d** (5 mmol) and $MeCOCH_2CO_2Et$ (5 mmol) in dry benzene (50 mL) in the presence of P-Me $C_6H_4SO_3H$ (0.05 g) was azeotropically refluxed for 2 h. The reaction was monitored by TLC with CH_2Cl_2/CH_3OH (39:1). After cooling to room temperature, the solvent was evaporated *in vacuo*, and the solid product formed, which was then purified by column chromatography CH_2Cl_2/CH_3OH (39:1) to obtain compounds **4 a–d**.

3-(3-Cyano-1,5-diphenyl-1H-Pyrrol-2-ylamino)-but-2-enoic acid ethyl ester (**4 a**)

Yield (58.3 %); mp 152–153 °C; IR (cm^{-1}) (KBr): 3436, 3239, 3061, 2970 (NH); 2227 (CN); 1654 (CO); ^{1}H-NMR ($CDCl_3$-d_3): 1.25 (t, 3 H, CH_2-CH_3), 1.80 (s, 3 H, CH_3), 4.10 (q, 2 H, CH_2), 4.70 (s, 1 H, CH), 6.60 (s, 1 H, 4-H), 7.00–7.50 (m, 10 H, $H_{arom.}$), 9.99 (br s, 1 H, NH); ^{13}C-NMR ($CDCl_3$-d_6): 14.37 (CH_3), 19.48 (CH_3), 59.10 (CH_2), 89.12 (CH), 91.17 (C_3), 109.64 (C_4), 115.62 (CN), 127.60–135.88 (arom.), 158.24 (NHC-), 169.93 (CO); EI MS m/z 371 (M^+).

3-[5-(4-Bromo-phenyl)-3-cyano-1-phenyl-1H-Pyrrol-2-ylamino]-but-2-enoic acid ethyl ester (**4 b**)

Yield (78 %); mp 145–146 °C; IR (cm^{-1}) (KBr): 3435, 3249, 2982 (NH); 2226 (CN); 1661 (CO); ^{1}H-NMR ($CDCl_3$-d_3): 1.25 (t, 3 H, CH_2-CH_3), 1.90 (s, 3 H, CH_3), 4.10 (q, 2 H, CH_2), 4.75 (s, 1 H, CH), 6.60 (s, 1 H, 4-H), 6.90–7.40 (m, 9 H, $H_{arom.}$), 9.90 (br s, 1 H, NH); ^{13}C-NMR ($CDCl_3$-d_6): 14.35 (CH_3), 19.45 (CH_3), 59.14 (CH_2), 89.36 (CH), 91.22 (C_3), 109.95 (C_4), 115.39 (CN), 121.84–135.37 (arom.), 157.98 (NHC-), 169.92 (CO); EI MS m/z 449 (M^+ – 1), 451 (M^+ + 1).

3-[3-Cyano-5-(4-methoxy-phenyl)-1-Phenyl-1H-pyrrol-2-ylamino]-but-2-enoic acid ethyl ester (**4 c**)

Yield (62.4 %); mp 160–161 °C; IR (cm^{-1}) (KBr): 3434, 3249, 2979 (NH); 2225 (CN); 1661 (CO); ^{1}H-NMR ($CDCl_3$-d_3): 1.20 (t, 3 H, CH_2-CH_3), 1.90 (S, 3 H, CH_3), 3.69 (S, 3 H, CH_3); 4.08 (q, 2 H, CH_2), 4.71 (s, 1 H, CH), 6.50 (s, 1 H, 4-H); 6.70–7.37 (m, 9 H, $H_{arom.}$), 9.97 (br s, 1 H, NH); ^{13}C-NMR ($CDCl_3$-d_6): 14.36 (CH_3), 19.45 (CH_3), 55.14 (OCH_3), 59.04 (CH_2), 88.94 (CH), 90.97 (C_3), 108.95 (C_4), 115.71 (CN), 123.32–135.69 (arom.), 158.35 (NHC-), 169.90 (CO); EI MS m/z 401 (M^+).

3-[3-Cyano-5-(4-fluoro-phenyl)-1-phenyl-1H-pyrrol-2-ylamino]-but-2-enoic acid ethyl ester (**4 d**)

Yield (47.80 %); mp 137–138 °C; IR (cm^{-1}) (KBr): 3435, 3240, 2986 (NH), 2227 (CN), 1655 (CO); ^{1}H-NMR ($CDCl_3$-d_3) 1.24 (t, 3 H, CH_2-CH_3), 1.90 (s, 3 H, CH_3), 4.14 (q, 2 H, CH_2), 4.30 (S, 1 H, CH), 6.60 (s, 1 H, 4-H), 6.90–7.41 (m, 9 H, $H_{arom.}$), 9.95 (br s, 1 H, NH); ^{13}C-NMR ($CDCl_3$-d_6): 14.35 (CH_3), 19.46 (CH_3), 59.12 (CH_2), 89.23 (CH), 91.14 (C_3), 109.56 (C_4), 115.50 (CN), 126.98–135.87 (arom.), 158.12 (NHC-), 163.70 (C-F), 169.92 (CO); EI MS m/z 389 (M^+).

General procedure for the preparation **5 a–d**

To propenylaminopyrroles **4 a–d** (5 mmol) in absolute ethanol (50 mL) metallic sodium (5 mmol) was added. Then the reaction mixtured was refluxed for 3 h. The reaction was monitored by TLC with CH_2Cl_2/CH_3OH (39:1). After cooling to room temperature, white precipitate of compounds **5 a–d** were obtained and then purified by column chromatography CH_2Cl_2/CH_3OH (39:1).

4-Amino-6-methyl-1,2-diphenyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester (**5 a**)

Yield (60.1 %); mp 207–208 °C; IR (cm^{-1}) (KBr): 3441 (NH_2), 1670 (CO); ^{1}H-NMR (DMSO-d_6): 1.31 (t, 3 H, OCH_2-CH_3), 2.55 (s, 3 H, CH_3), 4.29 (q, 2 H, CH_2), 6.95 (s, 2 H, NH_2), 7.22–7.53 (m, 11 H, $H_{arom.}$ and pyrrole-3-CH); ^{13}C-NMR (DMSO-d_6): 14.11 (CH_3), 26.88 (CH_3), 60.02 (CH_2), 100.93, 101.43 105.80, 127.20–136.80 (arom.) 149.93; 155.20, 161.81, 168.71; EI-MS m/z 371 (M^+). Anal. Calcd. ($C_{23}H_{21}N_3O_2$ 1.5 H_2O): C, 69.32; H, 5.32; N, 10.54. Found: C, 69.28; H, 5.51; N, 10.37.

4-Amino-2-(4-bromo-phenyl)-6-methyl-1-phenyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester (**5 b**)

Yield (85.80 %); mp 215–216 °C; IR (cm^{-1}) (KBr): 3427, (NH_2), 1670 (CO); ^{1}H-NMR (DMSO-d_6): 1.33 (t, 3 H, OCH_2-CH_3), 2.58 (s, 3 H, CH_3), 4.31 (q, 2 H, CH_2), 6.92 (s, 2 H, NH_2), 7.09–7.43 (m, 10 H, $H_{arom.}$ and pyrrole-3-CH); ^{13}C-NMR (DMSO-d_6): 14.05 (CH_3), 26.84 (CH_3), 60.06 (CH_2), 100.91, 101.51, 106.40, 122.34–136.72 (arom.) 149.61, 155.31, 161.85, 168.75; EI-MS m/z 449 (M^+ – 1), 451 (M^+ + 1) Anal. Calcd. ($C_{23}H_{20}BrN_3O_2$ 0.75 H_2O): C, 59.55; H, 4.35; N, 9.06. Found: C, 59.65; H, 4.4; N, 8.94.

4-Amino-2-(4-methoxy-phenyl)-6-methyl-1-phenyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester (**5 c**)

Yield (55.30 %); mp 199–200 °C; IR (cm^{-1}) (KBr): 3458, (NH_2), 1669 (CO); ^{1}H-NMR (DMSO-d_6): 1.32 (t, 3 H, OCH_2 CH_3), 2.57 (s, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 4.34 (q, 2 H, CH_2), 6.85 (s, 2 H, NH_2), 7.09–7.45 (m, 10 H, $H_{arom.}$ and pyrrole-3-CH); ^{13}C-NMR (DMSO-d_6) :14.08 (CH_3), 26.86 (CH_3), 59.95 (CH_2), 99.79, 101.33, 105.74, 113.75-136.81 (arom.) 149.67, 154.72, 161.95, 168.70; EI-MS m/z 401 (M^+). Anal. Calcd. ($C_{24}H_{23}N_3O_3$ H_2O): C, 68.66; H, 5.48; N, 10.10. Found: C, 68.67; H, 5.59; N, 9.95.

4-Amino-2-(4-fluoro-phenyl)-6-methyl-1-phenyl-1H-pyrrolo[2,3-b] pyridine-5-carboxylic acid ethyl ester (**5 d**)

Yield (48.60 %); mp 210–211 °C; IR (cm^{-1}) (KBr): 3437 (NH_2), 1672 (CO); ^{1}H-NMR (DMSO-d_6): 1.30 (t, 3 H, OCH_2CH_3), 2.58 (s, 3 H, CH_3), 4.26 (q, 2 H, CH_2), 6.90 (s, 2 H, NH_2), 7.10–7.48 (m, 10 H, $H_{arom.}$ and pyrrole-3-CH); ^{13}C-NMR (DMSO-d_6): 14.03 (CH_3), 26.82 (CH_3), 59.89 (CH_2), 100.84, 101.43, 105.70, 127.22-136.55 (arom.) 149.87, 155.20, 161.92, 168.63; EI-MS m/z 389 (M^+). Anal. Calcd. ($C_{23}H_{20}FN_3O_2$ H_2O): C, 67.74; H, 4.91; N, 10.31. Found: C, 67.85; H, 5.10; N, 10.22.

Biological methods

Rat TNF-α release assay

Compounds to be tested were administrated orally to the albino rats 30 min prior to LPS (0.1 mg/kg ip) challenge. Serum TNF-α levels were determined 90 min. after LPS injection as described in the literature [22]. Results represent means ±S.E.M. (n = 3).

Rat dose

Three rats were dosed orally (10 mg/kg) with a suspension of compound in methylcellulose 0.8 mg/mL (1 mg/kg) as described in the literature [22].

Rat

Male albino rats, weight, appr. 200 g.

Reagents

Lipopolysaccharides from *Escherichia coli* sero-type 026:B6 (LPS), from Sigma Chemical (St.Louis, MO, USA). Human TNF-α was obtained from Biosource International, Camarillo, CA, USA.

TNF-α assay method

Pre-coated goat anti-rabbit antibodies are used to capture a specific TNFα complex in each sample consisting of TNF-α antibody, biotinylated TNF-α, and sample/standard. Biotinylated TNF-α conjugate (competitive ligand) and sample or standard form a competition reaction for TNF-α specific antibody binding sites. Therefore, as the concentration of TNF-α in the sample increases, the amount of biotinylated TNF-α captured by the antibody decreases. With the addition of streptavidin conjugated alkaline phosphatase (which binds only to the biotinylated TNF-α) followed by the addition of the color reagent solution, the amount of biotinylated TNF-α is detected. This results in an inverse relationship between Optical Density (OD) and concentration: the higher the OD the less TNF-α in the sample.

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