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ORIGINAL RESEARCH

Synthesis, single crystal X-ray studies and antimicrobial activities of novel Indole barbiturates

S. Vijaya Laxmi · B. Janardhan · B. Rajitha · P. Raghavaiah · Prathima Srinivas

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Abstract A novel series of *N*-substituted 2-phenyl indole derivatives incorporating barbituric acid have been synthesised and the chemical structures of the resulting molecules were characterised by means of IR, NMR and mass spectra. The antimicrobial activities of these compounds were investigated. Significant improvement in the antimicrobial activity can be achieved, in the presence of Cl and Br substituents on phenacyl moiety at *para* position. Single crystal X-ray analysis was also performed for the compound **6b** in order to determine the crystal structure.

Keywords Antimicrobial activity · Barbituric acid · Crystal structure · 2-Phenyl-1*H*-Indole-3-carbaldehyde

Introduction

Indole, a potent basic pharmacodynamic nucleus, has been reported to possess a wide variety of biological properties, viz., anti-inflammatory (Preeti Rani *et al.*, 2004), anticancer (Jing-Ru Weng *et al.*, 2010; Mahboobi *et al.*, 2005), antidepressant (Kar and Attah, 1991), antibacterial (Tiwari *et al.*, 2006; Deepa Sinha *et al.*, 2008), and antifungal (El-Sawy *et al.*, 2006). Moreover, as an important class of organic heterocyclic dyes, indole derivatives exhibit unique photo responsive organic compounds (Yukinori Nagao *et al.*, 2007; Anon, 1971) which render them useful in a variety of applications such as in light-emitting electrochemical cells, (Qianqian Li *et al.*, 2009) solid-state lasers, light-emitting diodes, fluorescent labels, and probes in biology and medicine, (Asefa and Singh, 2010; Lengvinaite *et al.*, 2010; Chao Zhang *et al.*, 2010). On the other hand, barbituric acid has been used as disperse dye with strong fluorescent and as yellow organic pigment (Theford *et al.*, 2003; Karci, 2008; Wang and Kim, 2009). In continuation of our studies on antimicrobial agents (Vijaya Laxmi *et al.*, 2011; Suresh kuarm *et al.*, 2011) we assessed antibacterial and antifungal activity of indole barbituric acid derivatives.

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Results and discussion

Synthesis of indole barbiturates

The synthesis of Indole-based barbituric acid derivatives were carried out according to Scheme 1. The key intermediate **1** (2-phenyl Indole) was synthesised based on literature method (Vogel's, 2006).

2-Phenyl-1*H*-indole on vilsmeier formylation-afforded compound **2**, (2-phenyl-1*H*-indole-3-carbaldehyde). When 2-phenyl-1*H*-indole-3-carbaldehyde is treated with simple, substituted phenacyl bromides, and alkyl bromides separately under K_2CO_3 and phase transfer catalytic conditions (PTC) with TBAB (tetra butyl ammonium bromide) in DMF stirring at room temperature-afforded compounds **3**(**a**–**e**) and **4**(**a**–**c**), respectively (Vijaya Laxmi and Rajitha, 2010). Further Knoevenegal condensation of intermediates **3**(**a**–**e**) and **4**(**a**–**c**) with barbituric acid in methanol under reflux furnished both alkyl and aryl indole barbiturates (**5a**–**e**) and

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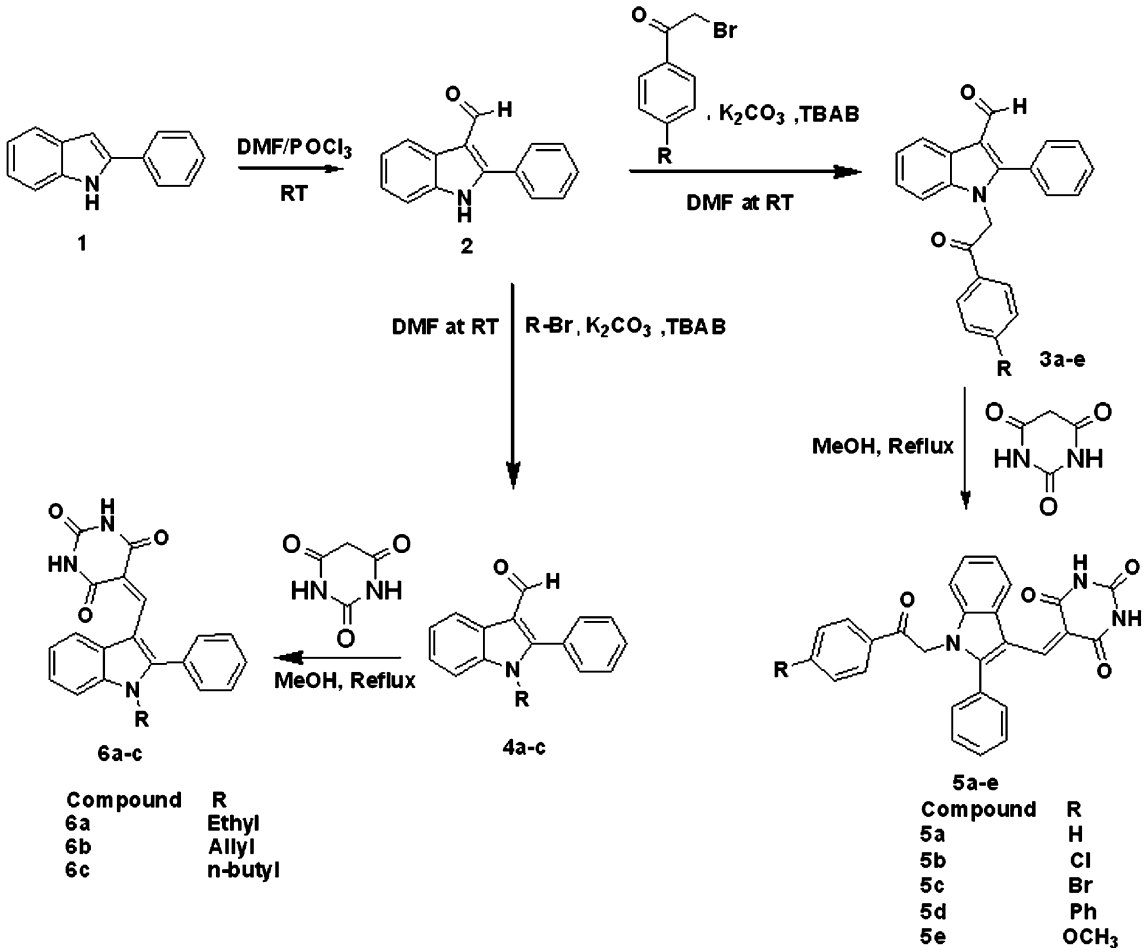

Scheme 1 Synthesis of indole barbiturates

(**6a–c**) in good yields. The Indole aldehydes **3**(**a–e**) and **4**(**a–c**) were colourless when condensed with barbituric acid the compounds **5**(**a–e**) and (**6a–c**) have shown yellow and orange colours. We have ascribed structure **5**(**a–e**) and (**6a–c**) by spectral analysis. In the IR spectra, bands in the region 3,180–3,220 cm^{-1} is attributed to NH of barbituric acid, bands at 1,727 and 1,680 cm^{-1} confirmed the presence of C=O group. In ^{1}HNMR spectrum C=C–H, NH protons of barbituric acid appeared as a singlet at δ ppm 7.9, 11.1, and 11.2, respectively. All other aromatic and aliphatic protons were observed at the expected region. In ^{13}C-NMR spectra, signal at δ 161.4–162.4 and 163.9–164.1 ppm assign the C=O groups in barbituric acid, while C=O of phenacyl group appeared in the range of 191.5–192.9 ppm (**5a–e**). EIMS and HRMS of the given compounds displayed (m^{+1}) and (m^{+23}) peaks, which confirmed their molecular weights.

X-ray crystallography

Prism-shaped single crystals of **6b** were obtained from a mixture of 1:1 ratio of chloroform and methanol by slow evaporation. Single crystal X-ray diffraction data was collected on a CCD detector based diffractometer-SMART APEX from Bruker-Nonius AXS using Mo-Kα radiation ($\lambda = 0.71073$ Å) at $T = 293(2)$. The crystal structure was solved by direct methods using SHELXS-97 program and refinements of F^2 were performed using SHELXL-97 program. A summary of the crystallographic data and structure refinement details are given in Table 1. The ORTEP representation of the molecular structure of **6b** is shown in Fig. 1. The crystal structure of **6b** consists of methanol sitting on the inversion center and water molecule.

Antimicrobial activity

The compounds were evaluated for antibacterial and anti-fungal activities, according to standard cup plate method (Granade and Artis, 1980). Nutrient broth and nutrient agar were used and samples dissolved in 5 ml of dimethyl-sulphoxide (DMSO). The solvent control DMSO did not show any antimicrobial activity. The antimicrobial activity

Table 1 Crystal data and summary of intensity data collection and structure refinement for compound **6b**

Empirical formula	$C_{45}H_{38}N_6O_{10}$
Formula weight	822.81
Temperature	293(2)
Crystal system, space group	Triclinic, *P*-1
Crystal description and colour	Prism, yellow colour
Unit cell parameters (Å,°)	
	$a = 10.2849$ (13)
	$b = 10.4038$ (13)
	$c = 11.8742$ (13)
	$\alpha = 99.067$ (10)
	$\beta = 101.513$ (10)
	$\gamma = 118.802$ (13)
Volume (Å^3)	1042.3(2)
Z	1
Crystal dimensions (mm)	0.42 × 0.32 × 0.28
D_{calc} (Mg/m^3)	1.311
F (0 0 0)	430
Absorption coefficient	0.094 mm^{-1}
Diffraction radiation wavelength (Å)	0.71073
Reflections collected/unique	7625/4244 [*R*(int) = 0.0330]
Extinction coefficient	0.010(3)
Max. and min. transmission	0.9741 and 0.9614
Limiting indices	$-12 \le h \le 12$, $-12 \le k \le 12$, $-12 \le l \le 14$
R indices (all data)	$R1 = 0.1291$, w$R2 = 0.1745$
2θ range for data collection (°)	2.89–26.37
Number of reflections	4244
Completeness to theta = 26.37	99.9%
Refined parameters	293
No. observed reflections	$I > 2$ s (I) 2406
Goodness-of-fit on F^2	1.047
Refinement Method	Full-matrix least-squares on F^2
CCDC	816380

was compared with known standard drugs at the same concentration. The known concentrations of Ampicillin and Ketoconazole (100, 200, 300 µg/ml) were used as standard for bacteria and fungi, respectively. The test cultures used were *Eschereschia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeuroginosa*, *Proteus vulgaris*, *Saccharomyces cerevesiae*, and *Candida albicans*. The results from the Table 2 reveals that the compounds **5**(**a**–**e**) and **6**(**a**–**c**) exhibited antimicrobial activity at 100–300 µg/ml concentration. In both the series **5b**, **5c**, **5d**, **6b**, and **6c** displayed marked antibacterial activity. Ampicillin was active as antibacterial agent and Ketoconazole as antifungal agent, whereas compounds **5b**, **5c**, **5d**, and **6b** showed remarkable antibacterial and antifungal activities, while compounds **5a** and **5e** were inactive towards bacteria and fungi.

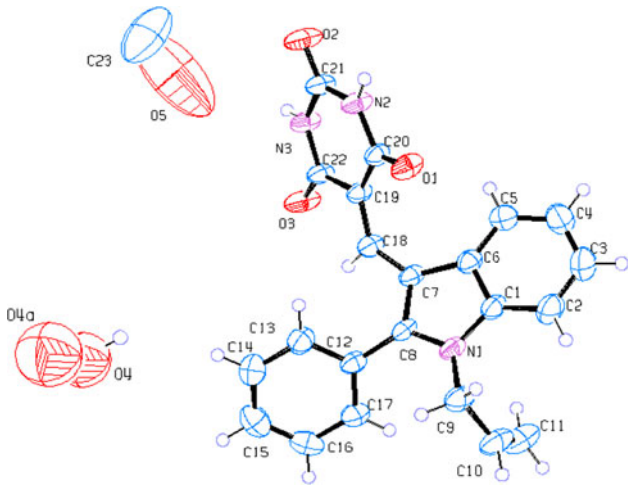

Fig. 1 ORTEP representation of compound **6b**

Conclusion

In this study, 2-phenyl indole barbituratic acid derivatives (**5a**–**e** and **6a**–**c**) were synthesised, identified by spectral data and single crystal X-ray analysis (**6b**). Antimicrobial activity of Indole barbiturates enhanced when chloro and bromo substituents introduced into aryl moiety in **5b** and **5c**, respectively, while the activity was found to be diminished in **5e** due to the introduction of methoxy group. From the results, we propose that the newly synthesised Indole barbiturates **5b**, **5c**, and **6b** can be considered as the lead compounds for the development as potential antimicrobial agents in the treatment of different bacterial and fungal infections.

Experimental

General

Chemicals were purchased from Merck (purity 98%). All melting points were determined with Quimis apparatus (Model Q-340s 13) and were uncorrected. TLC was performed on 2.0 × 6.0 cm aluminium sheets covered with silica gel (Sorbent, with 200 µm thickness) under ultraviolet radiation. Ethyl acetate:Hexane (2:8) is used as a mobile phase. Infrared (IR) spectra were obtained with ABB spectro photometer (Model: FTLA 2000-100) using KBr pellets. NMR, was measured on Brucker 300-MHz spectrometer using DMSO as a solvent and TMS as internal standard. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

Table 2 In vitro antimicrobial activity (MIC) values for compounds **5a–e** and **6a–c**

Bacterial strains						Fungal strains	
Compound	*E. coli*	*B. subtilis*	*S. aureus*	*P. aeuroginosa*	*P. vulgaris*	*S. cerevesiae*	*C. albicans*
μg/ml	100, 200, 300	100, 200, 300	100, 200, 300	100, 200, 300	100, 200, 300	100, 200, 300	100, 200, 300
5a	− − −	− − −	− − −	+ + +	+ − +	+ + ++	− − −
5b	++ ++ ++	+ + ++	+ + +	+ + +	+ + +	+ + ++	+ + +
5c	+ + ++	+ + ++	+ + +	+ + +	+ + +	++ ++ ++	+ + ++
5d	+ + ++	+ + +	+ + +	− − +	− + +	+ + ++	− − −
5e	− − −	− − +	− − −	+ + +	+ + +	− − +	+ + +
6a	− − −	− − +	− − −	+ + +	− − −	+ + +	++ + +
6b	+ ++ ++	+ ++ ++	++ ++ ++	+ + ++	+ + +	+ + +	++ ++ ++
6c	++ ++ ++	+ + ++	+ + +	− − −	+ + +	− − −	+ + +
Am	++ ++ ++	++ ++ ++	++ ++ ++	++ ++ ++	++ ++ ++	ND	− − −
Kt	ND	ND	ND	ND	ND	++ ++ ++	++ ++ ++

− resistant, + moderately sensitive, ++ sensitive

Am ampicillin, *Kt* ketoconazole, *ND* not done

General synthetic procedure for the compounds 5a–e and 6a–c

Derivatives of 1-(2-oxo-2-phenyl–ethyl)-2-phenyl-1*H*-indole-3-carbaldehyde (**3a–e**) or derivatives of 1-alkyl-2-phenyl-1*H*-indole-3-carbaldehyde (**4a–c**) (1.0 mol) were dissolved in methanol. An equimolar amount of barbituric acid was added to it, and the mixture was heated under reflux for 3–4 h. Product formation was confirmed by TLC, the mixture was cooled and the solid obtained was filtered and washed well with cold methanol. The characterisation data of compounds **5**(**a–e**), **6**(**a–c**) is given below.

Structural confirmations

*5-[1-(2-Oxo-2-phenyl–ethyl)-2-phenyl-1H-indol-3-ylmethylene]-pyrimidine-2,4,6-trione (**5a**)*

Orange solid; M.P 265–270°C; IR (KBr, υ_{max}, cm^{-1}): 3184, 3118 (N–H), 3054,(aromatic C–H) 2936 (aliphatic C–H), 1732, 1696 1665 (C=O), 1539, 1442,1299, 1202, 933, 749; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 5.96 (s, 2H), 7.19–8.20 (m, 9H),7.381(d,1H, $J = 5.2$ Hz), 7.546 (d, 1H, $J = 8$ Hz),7.61 (d, 1H, $J = 8$ Hz), 7.636(d,1H, $J = 5.2$ Hz), 7.98 (s,1H), 8.053(d,1H, $J = 7.2$ Hz), 11.02 (s, 1H, NH), 11.08(s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 51.5, 111.2, 111.9, 113.1, 121.5, 123.3, 124.6, 125.0, 128.2, 128.5, 128.7, 128.9, 130.2, 130.7, 134, 134.2, 138.3, 147.1, 150, 151.8, 161.4, 164, 193.4. MS HRMS: calculated *m/z* 449.14 found 449.056, 450.059 (m + 1), 472.044 (m + 23) For the M.F $C_{27}H_{19}N_3O_4$.

*5-{1-[2-(4-Chloro-phenyl)-2-oxo-ethyl]-2-phenyl-1H-indol-3-ylmethylene}-pyrimidine-2,4,6-trione (**5b**)*

Yellowish solid; M.P 250–255°C; IR (KBr, υ_{max}, cm^{-1}): 3188,3086(N–H), 3050, (aromatic C–H) 2916, (aliphatic C–H), 1735, 1694, 1656 (C=O), 1532, 1442, 1227, 1198, 930, 747; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.97(s, 2H), 7.2–8.0 (m, 9H), 7.373 (d, 1H, $J = 6$ Hz),7.586(d, 1H, $J = 6$ Hz), 7.681(d, 1H, $J = 8.4$), 7.98 (s, 1H), 8.081(d, 1H, $J = 8.8$), 11.05(s, 1H, NH),11.11(s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 51.6, 111.2, 112.0, 113.1, 121.5, 123.3, 124.6, 125.0, 128.5, 128.7, 129.0, 130.1, 130.2, 132.6, 138.2, 139.2, 147.1, 150.4, 151.7, 161.4, 164.0, 192.6. MS ESI: 484 (m + 1) (10%). For the M.F $C_{27}H_{18}ClN_3O_4$, M.Wt 483.

*5-{1-[2-(4-Bromo-phenyl)-2-oxo-ethyl]-2-phenyl-1H-indol-3-ylmethylene}-pyrimidine-2,4,6-trione (**5c**)*

Yellowish solid; M.P 235–240°C; IR (KBr, υ_{max}, cm^{-1}): 3216, 3079 (N–H), 3057, (aromatic C–H) 2923(aliphatic C–H), 1725, 1686,1652(C=O), 1577, 1424, 1228, 1098, 931,750; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.96 (s, 2H), 7.27–7.97. (m, 9H), 7.289(d, 1H, $J = 5.2$ Hz), 7.365 (d,1H, $J = 6$ Hz), 7.564 (d,1H, $J = 5.2$ Hz), 7.819 (d,1H, $J = 8.8$ Hz), 7.98 (s, 1H), 11.03(s, 1H, NH), 11.10(s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 51.6, 111.3, 112.1, 113.2, 121.6, 123.4, 124.7, 125.1, 128.5, 128.6, 128.8, 129.1, 130.3, 132.0, 138.3, 147.2, 150.5, 151.8, 161.5, 164.1, 192.8. MS ESI: 528 (m + 1) (100%). For the M.F $C_{27}H_{18}BrN_3O_4$, M.Wt 527.

*5-[1-(2-Biphenyl-4-yl-2-oxo-ethyl)-2-phenyl-1H-indol-3-ylmethylene]-pyrimidine-2,4,6-trione (**5d**)*

Orange solid; M.P 250–255°C; IR (KBr, υ_{max}, cm^{-1}): 3225, 3192 (N–H), 3070(aromatic C–H), 2929(aliphatic C–H), 1709, 1672,1665(C=O), 1538, 1447, 1284, 1187, 944, 753; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6(s, 2H), 7.3–7.76 (m, 16H), 7.89(d, 1H, $J = 8.4$ Hz) 7.99 (s, 1H), 8.147 (d, 1H, $J = 8.4$ Hz), 11.03(s, 1H, NH), 11.09(s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 51.6, 111.2, 111.9, 113.1, 121.5,123.3, 124.6, 125.1, 127.0, 128.5, 128.7, 128.9, 129.1, 130.2, 130.4, 130.7, 132.7, 138.3, 138.6, 145.6, 147.2, 150.4, 151.9, 161.4, 164.0, 192.9. MS ESI: 526 (m + 1) (10%). For the M.F $C_{33}H_{23}N_3O_4$, M.Wt 525.

*5-{1-[2-(4-Methoxy-phenyl)-2-oxo-ethyl]-2-phenyl-1H-indol-3-ylmethylene]-pyrimidine-2,4,6-trione (**5e**)*

Yellowish solid, M.P 265–270°C, IR (KBr, υ_{max}, cm^{-1}): 3179, 3104, (N–H) 3030(aromatic C–H), 2932(aliphatic C–H), 1729, 1693, 1650(C=O),1513, 1440, 1220, 1081, 938, 760. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.8 (s, 3H) 5.8 (s, 2H), 7.0–8.0 (m, 10H), 7.565 (d, 1H, $J = 6$ Hz), 7.101 (d, 1H, $J = 8.8$ Hz), 7.97 (s, 1H), 8.041 (d,1H, 8.8 Hz), 11.02 (s, 1H, NH), 11.08 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 51.2, 55.6, 111.2, 111.8, 113.1, 114.1, 121.5, 123.3, 124.6, 125.0, 126.8, 128.5, 128.7, 130.2, 130.6, 130.7, 138.3, 147.2, 150.4, 152.0, 161.4, 163.9, 164.0, 191.5. MS ESI: 502 (m + 23) (60%). For the M.F $C_{28}H_{21}N_3O_5$, M.Wt 479.

*5-(1-Ethyl-2-phenyl-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (**6a**)*

Orange Solid; M.P 245–250°C; IR (KBr, υ_{max}, cm^{-1}): 3170, 3090(N–H), 3040(aromatic C–H), 1721,1685 (C=O), 1536, 1484, 1231, 936, 758; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.289 (t, $J = 6.8$ Hz, 3H, CH_2–CH_3), 4.289 (q, $J = 6.8$ Hz, 2H, CH_2-CH_3), 7.26–7.7 (m, 9H), 7.93 (s, 1H), 10.95(s, 1H, NH),11.02(s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 36.5, 47.9, 110.9, 111.3, 112.7,121.5, 123.3, 124.8, 125.2, 128.7, 130.1, 131.0, 137.3, 147.3, 150.4, 151.9, 162.4, 163.1. MS ESI 360 (m + 1) (50%). For the M.F $C_{21}H_{17}N_3O_3$ M.Wt 359.

*5-(1-Allyl-2-phenyl-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (**6b**)*

Yellowish solid; M.P 220–225°C; IR (KBr, υ_{max}, cm^{-1}): 3186(N–H), 3050, 2831, 1729, 1686 (C=O), 1530, 1440, 1225, 943, 746; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.866 (d, $J = 3.6$ Hz, 2H, CH_2–CH),4.950–4.907 (d, $J = 17.2$,1H, H–C=C–H trans) 5.195(d, 1H, $J = 10.4$, H–C=C–H cis), 6.024 (m, 1H) 7.25–7.65 (m, 9H), 7.96 (s, 1H), 10.98 (s,1H, NH), 11.05 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 46.9, 48.5, 111.5, 111.6, 112.9, 117.2, 121.6, 123.3, 124.7, 125.2, 128.7, 130.2, 130.9, 133.0, 137.4, 147.3, 150.4, 151.4, 161.4, 164. MS ESI 371 (m +) (40%), 372(m + 1) (20%). For the M.F $C_{22}H_{17}N_3O_3$ M.Wt 371.

*5-(1-Butyl-2-phenyl-1H-indol-3-ylmethylene)-pyrimidine-2,4,6-trione (**6c**)*

Orange solid; M.P 220–230°C; IR (KBr, υ_{max}, cm^{-1}): 3203, 3080 (N–H), 2931 (aliphatic C–H), 1727, 1688 (C=O), 1550, 1443, 1295, 970, 749; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.691 (t, $J = 7.2$ Hz, 3H, CH_3–CH_2), 1.07 (m, 2H), 1.58 (m, 2H), 4.272 (t, $J = 7.2$ Hz, 2H, CH_2–CH_2), 7.2–7.7 (m, 9H), 7.9 (s, 1H), 10.96 (s, 1H, NH), 11.03 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.1, 19.1, 31.0, 43.9, 110.9, 111.3, 112.9, 121.5, 123.3, 124.9, 125.2, 128.7, 130.1, 131.0, 137.3, 147.3, 150.4, 151.9, 161.4, 164.1. MS HRMS Calculated 387.16 found 387.084, 388.09 (m + 1), 410.077 (m + 23) For the M.F$C_{23}H_{21}N_3O_3$.

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Declaration of interest The author reports no conflicts of interest. The author alone hereby stands responsible for the contents of this scientific paper.

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