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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis characterization and biological evaluation of some alkoxyphthalimide derivatives of 3-(4-substituted phenyl)-6, 6-diphenyl-3,3a-dihydro-2*H*-imidazo[2,1-*b*]pyrazolo[3,4-*d*] [1,3]thiazol-7(6*H*)-one

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Abstract A series of 2-*N*-ethoxyphthalimido 3-(4-substitutedphenyl)-6,6-diphenyl-3,3a-dihydro-2H-imidazo[2,1-*b*] pyrazolo[3,4-*d*][1,3]thiazol-7(6H)-one(**7a–e**) and 4-(4-substituted phenyl)-2-(*N*-ethoxyphthalimido amino)-7,7-dipheny-limidazo[2′,1′:2,3][1,3]thiazolo[4,5-*d*] pyrimidin-8(7H)-one (**9a–e**) have been designed and synthesized starting from thiohydentoin (**1**). The structure of all synthesized compounds has been established by IR, ^{1}H NMR, ^{13}C NMR and mass studies. These compounds have been screened for antimicrobial activities in order to evaluate the possibility of the derivatives to be used as potential chemotherapeutic agents.

Keywords Imidazole · Thiazole · Pyrazole · Pyrimidine · Antimicrobial activity

Introduction

Imidazole derivatives have evoked considerable attention in recent years as these are endowed with a wide range of pharmaceutical activities like antifungal (Enguehard *et al.*, 2000), antihypertensive (Hadizadeh *et al.*, 2005), IL-1 inhibitor (Chang *et al.*, 2001), antioxidant (Goker *et al.*, 2002), cardiotonic (Insuasty *et al.*, 2002), antithrombotic (Zhou *et al.*, 2005) anticonvulsant (Shafiee *et al.*, 2004), antihepatitis B and C virus activity (Zhang *et al.*, 2005), etc. Thiazoles and their derivatives are found in many natural and synthetic products with a wide spectrum of biological activities such as antibacterial (Hans, 1978), antifungal (Wilson *et al.*, 2001), anti-inflammatory (Berlin and Herd, 1991), antitumor activity (Kumar *et al.*, 1993) and cytotoxic activities (Plouvier *et al.*, 1995). The pyrazoline nucleus is a ubiquitous feature of pharmacological interest and has been proven to be a fertile source of medicinal agents such as cytotoxic (Bhat *et al.*, 2005), antiamoebic (Abid and Azam, 2005), antibacterial (Azarifar and Maseud 2002), cyclo-oxygenase-II (COX-IISS) (Kumar *et al.*, 2004), antiproliferative (Chimichi *et al.*, 2006) and anticancer (Tandon *et al.*, 2005). Pyrimidine derivatives serve both as biomimetic and reactive pharmacophores due to their diverse medicinal properties such as antitumor (Sasaki *et al.*, 2003), anticancer (lungs, breast and CNS cancer) (Sondhi *et al.*, 2001), immunodilator (Heiba *et al.*, 1998), antiviral (Nasr and Gineinah, 2002), etc. Pyrimidine derivatives have activities like tyrosine kinase inhibitors (Frey and Wishart, 2005), COX-2 inhibitor (Reddy *et al.*, 2005), calcium channel blockers plus antihypertensive (Kappe, 2004) and also activity against Y181C HIV-1 mutant strain (Gupta *et al.*, 2005), etc. Diverse biological activities like anticonvulsant (Loscher, 1946), diuretic (Cornish *et al.*, 1966), fungicidal (Kaunowasky *et al.*, 1966) and trypanocidal (Hayashi, 1956) have been observed for alkoxyphthalimide and related functionalities. The ability to inhibit growth of malarial parasite *Plasmodium falsiparum* (Mamalis, 1971) have also been observed for several aminoxy derivatives. Heterocyclic rings attached to alkoxyphthalimide group have been synthesized (Banu *et al.*, 2000) and tested for antimicrobial and antimalarial (Singh *et al.*, 2004) activity. We planned to undertake the synthesis and characterization of some imidazole derivatives carrying the above biodynamic heterocyclic systems with the hope to achieve enhanced biological activity.

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Results and discussion

Simple base catalyzed condensation of α-diketone (benzil), with thiourea in absolute ethanol followed by pinacol-pinacolone type rearrangement furnished to 5,5-diphenyl-2-thioxoimidazolidin-4-one (**1**) Formation of this product was confirmed appearance stretching bands in IR spectrum at 1705, 3294 cm^{-1} which indicates the presence of CONH group and 1215, 3236 cm^{-1} is for the presence of CSNH moiety and disappearance of NH_2 peak at 3367,3267. In ^{1}H-NMR spectrum shows two singlets at δ 9.90 and δ 9.10, which would be assigned for NH proton of amide. It was condensed with chloroacetic acid in glacial acetic acid presence of anhydrous sodium acetate to yielded the 6,6-diphenylimidazo[2,1-*b*][1,3]thiazole-3,5(2*H*,6*H*)-dione (**2**). Its structure was confirmed by appearance of singlet at δ 3.65 for CH_2 of thizole ring and disappearance of both NH signals in ^{1}H NMR spectra. This was condensed with various 4-substituted araldehydes in the presence of anhydrous sodium acetate in glacial acetic acid to give corresponding 2-(4-subsituted phenyle)-6,6-diphenylimidazo[2,1-*b*][1,3]thiazole-3,5(2*H*,6*H*)-dione derivatives (**4a–e**). Reaction of hydrazine hydrate on these compounds (**4a–e**) underwent cyclocondensation reaction afforded 3-(4-substituted phenyl)-6,6-diphenyl-3,3a-dihydro-2*H*-imidazo[2,1-*b*]pyrazolo[3,4-*d*][1,3]thiazol-7(6*H*)-one (**5a–e**). The structures of these compounds were inferred by IR absorption band at 3270 cm^{-1} and ^{1}H NMR spectra at δ 6.83 corresponding to the NH proton of the pyrazole ring. The N–H proton of (**5a–e**) was replaced by reaction with bromoalkoxyphthalimide (**6**) in ethanolic media using pyridine as base. The resulting product was identified as 2-*N*-ethoxyphthalimido 3-(4-substituted phenyl)-6,6-diphenyl-3,3a-dihydro-2*H*-imidazo[2,1-*b*]pyrazolo[3,4-*d*][1,3]thiazol-7(6*H*)-one (**7a–e**). The IR spectra of (**7a–e**) displayed strong absorption band for CO–N–CO group at around 1726–1705 cm^{-1}, while N–O and C–O bond give relatively weak absorption bands at 1492 and 1013 cm^{-1}, respectively. Disappearance of NH stretching band around 3270 cm^{-1} also confirmed the replacement of hydrogen of pyrazole by ethoxyphthalimide moiety, which was present in its precursor. Additional proof for the proposed structure of (**7a–e**) was provided by close observation of ^{1}H NMR spectra, which showed disappearance of NH signal at δ 6.2 and presence of new signals for NCH_2 and OCH_2 protons resonating at δ 3.75 and 4.44, respectively. In an another route (**4a–e**) when treated with guanidine nitrate in presence of concentrated ethanolic alkali gave 2-amino-4-(4-substitutedphenyl)-7,7-diphenyl-[4,5-*d*]pyrimidin-8(7*H*)-one (**8a–e**). Formation of Pyrimidine ring in **8a–e** was confirmed by IR spectra at 3212–3357 cm^{-1} and ^{1}H NMR spectra exhibited a singlet at δ 6.74 for NH_2 proton. These were further condensed with bromoalkoxyphthalimide (**6**) to yield the final compounds 4-(4-substituted phenyl)-2-(*N*-ethoxyphthalimidoamino)-7,7-diphenylimidazo[2′,1′:2,3][1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one (**9a–e**). Schematic presentation of reaction sequence is given in Scheme 1. Positive fluorescence test of **7a–e** and **9a–e** also confirmed the inclusion of alkoxyphthalimide chromophore in these molecules.

Antimicrobial activity

Ten synthesized compounds **7a–e** and **9a–e** were in vitro screened for their antibacterial and antifungal activity using cup or well method (Simmons, 1996). Antibacterial activity of the compounds (500 ppm im DMF media) have been evaluated against four bacterial strains viz., *Escherichia coli*, *Bacillus subtilis*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. The activity was measured as a function of zone of inhibition in mm. Results were compared with the reference drug ciprofloxacin by measuring their zone of inhibition and activity index (Table 1; Scheme 1).

All the compounds show poor activity against *B. subtilis* and *P. mirabilis* where as these show moderate to strong activity against *E. coli* and *P. aeruginosa*. Compound **9b** displayed activity index more then one against *E. coli* and **9c** against *P. aeruginosa*. Activity index of **9e** is comparable to the standard used against *E. coli* and *P. aeruginosa*. The same is also true for **7d** against *P. aeruginosa*. Moderate activity of compounds **7a**, **7b**, **7c**, **7e**, **9a**, **9c**, **9d** against *E. coli*, **7d**, **9c**, **9d** against B. *subtilis*, **9b** against *P. mirabilis*, **7b**, **7c**, **9a**, **9b** and **9d** against *P. aeruginosa* was observed. Overall antibacterial activity of synthesized compounds is moderate as compared to ciprofloxacin but when cefuroxime was used as a reference drug, the activity looks to be strong.

Screening of above compounds in a concentration of 500 ppm for antifungal activity by the same technology was carried out against two fungal strains viz., *Candida albicans* and *Aspergillus fumigates* using Amphotericin B as a control. It was pleasure to note that maximum number of compounds shows stronger activity then the standard used against *C. albicans*. Activity index for **7a**, **7b**, **7c**, **7d**, **7e**, **9b**, **9c**, **9d** and **9e** is more then one. Activity against *A. fumigates* using same control is insignificant (Table 1).

It may be concluded from the activity study that the synthesized compounds have high versatility in activity against various microbes viz., stronger against *C. albicans*, moderate against *E. coli* and *P. eruginosa*, weaker against *B. subtilis*, *P. mirabilis* and *A. fumigates*.

Table 1 Antimicrobial activity of the synthesized compounds **7a–e** and **9a–e**

Compd. no.	Antibacterial activity				Antifungal activity	
	Escherichia coli	Bacillus *subtilis*	*Proteus mirabilis*	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus fumigatus*
7a	11	4	5	9	20	6
	(0.68)	(0.25)	(0.31)	(0.50)	(1.17)	(0.60)
7b	12	9	3	14	19	4
	(0.75)	(0.52)	(0.18)	(0.77)	(1.11)	0.40)
7c	12	6	8	11	20	5
	(0.75)	(0.35)	(0.50)	(0.61)	(1.17)	(0.50)
7d	9	11	6	17	18	3
	(0.56)	(0.68)	(0.37)	(0.94)	(1.05)	(0.30)
7e	10	7	5	10	17	2
	(0.65)	(0.41)	(0.31)	(0.55)	(1.00)	(0.20)
9a	13	5	4	13	11	6
	(0.81)	(0.29)	(0.25)	(0.72)	(0.64)	(0.60)
9b	18	7	10	14	26	2
	(1.12)	(0.41)	(0.62)	(0.77)	(1.52)	(0.20)
9c	13	13	8	21	23	4
	(0.81)	(0.76)	(0.50)	(1.16)	(1.35)	(0.40)
9d	11	12	6	12	21	5
	(0.68)	(0.70)	(0.37)	(0.66)	(1.23)	(0.50)
9e	15	10	7	11	19	8
	(0.93)	(0.58)	(0.43)	(0.61)	(1.11)	(0.80)
C_1	16	17	16	18	17	10

Zone of growth inhbition (mm) (activity index)

(Activity index) = Inhibition zone of compound/Inhibition zone of the standard drug

For antibacterial activity: C_1 = ciprofloxacin

For antifungal activity: C_1 = amphotericin B

Experimental section

General procedures

All the melting points were determined in open capillary tube and are uncorrected. The IR spectra were recorded on Perkin–Elmer spectrometer. The ^{1}H NMR spectra were scanned on a DRX-300 MHz spectrometer (300 MHz) in $CDCl_3$/DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm. The mass spectra were recorded on jeol SX-102 (FAB). *m*-Nitrobenzyl alcohol (NBA) was used as a matrix. Purity of synthesized compounds was checked by TLC using silica gel-G. Spots were exposed in an iodine chamber. Compound **6** was synthesized by literature method (Bauer and Suresh, 1963).

*Synthesis of 5,5-diphenyl-2-thioxoimidazolidin-4-one (**1**)*

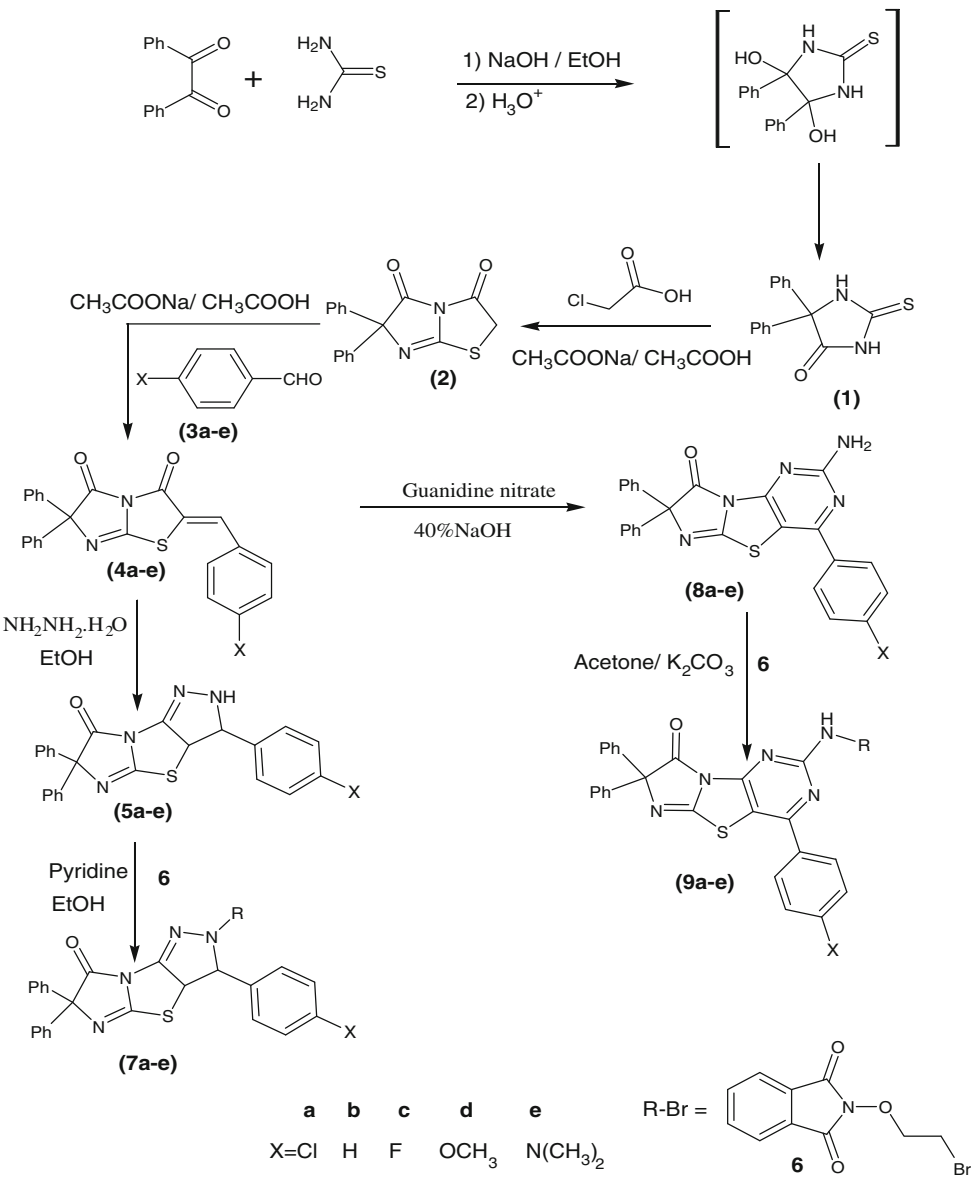
Benzil (0.05 mol), thiourea (0.05 mol) and 15 ml of 30% aq. NaOH was refluxed in 75 ml of ethanol for 2 h; it was allowed to cool and poured into crushed ice with constant stirring. The solid separated was filtered and the insoluble by product was removed. The filtrate was acidified with conc. HCl and the obtained precipitated solid was filtered, dried and recrystallized from ethanol.

Yield 94%, m.p. 136°C; IR (KBr) cm^{-1}: 3255 (N–H amide, CO–NH–CS); 3135 (N–H, CPh_2–NH–CS); 3010 (C–H Ar–H); 1705 (C=O); 1215 (C=S); ^{1}H NMR (DMSO d_6) δ: 6.97–7.69 (m, 3H, Ar–H), δ 9.90 (s, 1H, NH, CO–NH–CO); δ 9.10 (s, 1H, NH, CO–NH–CPh_2); ^{13}C-NMR (DMSO) δ: 180.65, 174.54, 139.70, 129.10, 128.78, 126.76, 73.87. Anal. calcd. for $C_{15}H_{12}N_2OS$: C, 67.16; N, 10.44; S, 11.94%. Found C, 67.08; N, 10.10; S, 11.75%; MS: *m/z* 268 [M]$^+$.

*Synthesis of 6,6-diphenylimidazo[2,1-b][1,3]thiazole-3, 5(2H,6H)-dione (**2**)*

A mixture of **1** (0.01 mol) and chloroacetic acid (0.01 mol) was dissolved in gl.acetic acid in presence (0.02 mol) anhydrous sodium acetate and was refluxed for 8 h. The reaction mixture was cooled and poured into cold ice water with stirring. The solid formed was filtered and crystallized from ethanol. Yield 89%, m.p. 162°C; IR (KBr) cm^1: 3045 (C–H Ar–H); 2952 (C–H, CH_2), 1695 (C=O), 1594 (C=N); ^{1}H NMR (DMSO d_6) δ: 7.85–7.67 (m, 10H, Ar–H),3.65 (s,CH_2, thizole); ^{13}C-NMR (DMSO d_6) δ: 167.21, 170.03, 162.56, 143.14, 129.23, 128.11, 126.10, 73.05, 32.70. Anal. calcd. for $C_{17}H_{12}N_2O_2S$: C, 66.32; N, 9.09; S, 10.38%. Found C, 66.02; N, 10.08; S, 10.05%; MS: *m/z* 308 [M]$^+$.

Scheme 1



*Synthesis of 2-(4-chlorobenzylidene)-6, 6-diphenylimidazo[2,1-b][1,3]thiazole-3, 5(2H,6H)-dione (**4a**)*

An equimolar mixture of 2 (0.01mol) and 4-chlorobenzalde-hyde 3a (0.01mol) in glacial acetic acid was taken in a round bottom flask and anhydrous sodium acetate (0.02 mol) was added and refluxed for 8 h. Reaction mixture was allowed to cool and solid separated was recrystallized from ethanol. Yield 84%, m.p. 189°C; IR (KBr) cm^{-1}: 3025 (C–H, Ar–H), 1691 (C=O), 1590 (C=N), 758 (C–Cl); ^{1}H NMR (DMSO d_6) δ: 7.62–7.76 (m, 14H, Ar–H), 6.12 (s, 1H, =CH–Ar); ^{13}C-NMR (DMSO d_6) δ: 171.05, 166.30,163.0, 142.05, 140.15, 132.23, 129.24, 128.80, 127.12, 126.35, 120.67, 80.05. Anal. calcd. for $C_{24}H_{15}ClN_2O_2S$; C, 66.97; N, 6.51, S, 7.44%. Found C, 66.54; N, 6.45; S, 7.24%; MS: *m/z* 430 $[M]^+$, 432 $[M + 2]^+$.

Compounds (**2b–e**) were also prepared by similar method with some change in reflux time and reaction work up. Their characteristic spectral and analytical data are given below:

*2-Benzylidene-6,6-diphenylimidazo[2,1-b][1,3]thiazole-3, 5(2H,6H)-dione (**4b**)*

Yield 81%, m.p. 180°C; IR (KBr) cm^{-1}: 3027 (C–H, Ar–H), 1693 (C=O), 1594 (C=N); ^{1}H NMR (DMSO d_6) δ: 7.56–7.64 (m, 14H, Ar–H), 6.09 (s, 1H, =CH–Ar); ^{13}C-NMR (DMSO d_6) δ: 170.60, 165.90, 162.85, 142.15, 139.63, 132.12, 129.04, 128.65, 127.10, 126.17, 120.20, 78.34. Anal. calcd.

for $C_{24}H_{15}N_2O_2S$; C, 72.72; N, 7.07; S, 8.08%. Found C, 72.54; N, 6.90; S, 7.89%; MS: *m/z* 396 $[M]^+$.

*2-(4-Flurobenzylidene)-6,6-diphenylimidazo[2,1-b] [1,3]thiazole-3,5-(2H,6H)-dione (**4c**)*

Yield 86%, m.p. 192°C; IR (KBr) cm^{-1}: 3037 (C–H, Ar–H), 1697 (C=O), 1597 (C=N), 1158 (C–F); ^{1}H NMR (DMSO d_6) δ: 7.65–7.84 (m, 14H, Ar–H), 6.16 (s, 1H, =CH–Ar); ^{13}C-NMR (DMSOd_6) δ:171.68, 166.10, 163.58, 142.85, 139.90, 132.65, 129.86, 128.96, 127.18, 126.67, 120.45, 78.94. Anal. calcd. for $C_{24}H_{15}FN_2O_2S$; C, 69.56; N, 6.76; S, 7.29%. Found C, 69.14; N, 6.35; S, 7.10%; MS: *m/z* 414$[M]^+$.

*2-(4-Methoxybenzylidene)-6,6-diphenylimidazo[2,1-b] [1,3]thiazole-3,5(2H,6H)-dione (**4d**)*

Yield 83%, m.p. 184°C; IR (KBr) cm^{-1}: 3028 (C–H, Ar–H), 1687 (C=O), 1589 (C=N), 1098 (C–O); ^{1}H NMR (DMSO d_6) δ:7.60–7.74 (m, 14H, Ar–H), 6.02 (s, 1H, =CH–Ar) 3.64 (3H, s, OCH_3); ^{13}C-NMR (DMSO d_6) δ: 170.46, 166.18, 163.18,141.35, 139.10, 132.25, 128.16, 127.93, 127.34, 125.97, 120.23, 56.78, 78.14. Anal. calcd. for $C_{25}H_{18}N_2O_3S$; C, 70.40; N, 6.27; S, 7.05%. Found C, 70.12; N, 6.05; S, 7.16%; MS: *m/z* 446 $[M]^+$.

*2-[4-(N,N-dimethylamino)benzylidene]-6, 6-diphenylimidazo[2,1-b][1,3]thiazole-3, 5(2H,6H)-dione (**4e**)*

Yield 87%, m.p. 182°C; IR (KBr) cm^{-1}: ^{1}3043 (C–H, Ar–H), 1681 (C=O), 1584 (C=N); ^{1}H NMR (DMSO d_6) δ: 7.57–7.34 (m, 14H, Ar–H), 6.14 (s, 1H, =CH–Ar), 3.15 (6H,s,N$(CH_3)_2$; ^{13}C-NMR (DMSO d_6) δ: 171.16, 166.10, 162.98, 141.45, 139.20, 132.53, 128.34, 127.83, 127.14, 125.65, 119.93, 56.43, 78.35, 43.78. Anal. calcd. for $C_{26}H_{21}N_3O_2S$; C, 71.07; N, 9.56; S, 7.28%. Found C, 69.98; N, 9.35; S, 7.02%; MS: *m/z* 439 $[M]^+$.

*Synthesis of 3-(4-chlorophenyl)-6,6-diphenyl-3,3a-dihydro-2H-imidazo[2,1-b]pyrazolo[3,4-d] [1,3]thiazol-7(6H)-one (**5a**)*

Compound **4a** (0.01 mol) and hydrazine hydrate (0.02 mol) were taken in absolute alcohol (20 ml) and a catalytic amount of acetic acid were added to it. It was refluxed for 8 h, cooled and poured into crushed ice. The product obtained was washed several times with water and then dried. It was recrystallized from alcohol. Yield 83%, m.p. 223°C; IR (KBr) cm^{-1}: 3270 (N–H str.) 3048 (C–H, Ar–H), 1726 (C=O), 1524 (C=N), 747 (C–Cl); ^{1}H NMR (DMSO d_6) δ: 7.1–7.8 (m, 14H, Ar–H), 6.83 (s, 1H, NH), 4.62 (d, 1H, –CH–Ar), 3.43 (d, 1H,–CH-S); ^{13}C-NMR (DMSO d_6) δ: 174.12, 154.16, 164.03, 144.02, 140.56, 139.23, 132.80, 129.20, 128.58, 128.89, 128.01, 12.27, 80.17, 48.10, 50.18. Anal. calcd. for $C_{24}H_{17}ClN_4OS$; C, 64.86; N, 12.61; S, 7.17%. Found C, 64.53; N, 12.20; S, 7.01%; MS: *m/z* 444$[M]^+$, 446 $[M + 2]^+$.

Same procedure was adopted for the synthesis of compound **(5b-e)**. Spectral data of these are mentioned below:

*3,6,6-Triphenyl-3,3a-dihydro-2H-imidazo [2,1-b]pyrazolo[3,4-d][1,3]thiazol-7(6H)-one (**5b**)*

Yield 79%, m.p. 216°C; IR (KBr) cm^{-1} 3265 (N–H str.) 3042 (C–H, Ar–H), 1724 (C=O), 1528 (C=N); ^{1}H NMR (DMSO d_6) δ: 6.9–7.6 (m, 14H, Ar–H), 6.78 (s, 1H, NH), 4.58 (d, 1H, –CH–Ar), 3.41 (d, 1H, –CH–S); ^{13}C-NMR (DMSO d_6) δ: 174.08, 154.10, 163.93, 143.82, 140.26, 139.12, 132.43, 129.03, 128.16, 128.29, 127.87, 126.02, 79.97, 47.10, 49.18. Anal. calcd. for $C_{24}H_{18}N_4OS$; C, 70.24; N, 13.65; S, 7.80%. Found C, 70.73; N, 13.40; S, 7.57%; MS: *m/z* 410$[M]^+$.

*3-(4-Fluorophenyl)-6,6-diphenyl-3,3a-dihydro-2H-imidazo[2,1-b]pyrazolo[3,4-d][1,3]thiazol-7(6H)-one (**5c**)*

Yield 82%, m.p. 231°C; IR (KBr) cm^{-1}. 3274 (N–H str.) 3049 (C–H, Ar–H), 1729 (C=O), 1537 (C=N), 1178 (C–F); ^{1}H NMR (DMSO d_6) δ: 7.2–7.8 (m, 14H, Ar–H), 6.82 (s, 1H, NH), 4.64 (d, 1H, –CH–Ar), 3.48 (d, 1H, –CH–S); ^{13}C-NMR (DMSO d_6) δ: 174.78, 154.56, 164.19, 144.18, 140.76, 139.67, 132.84, 130.13, 128.87, 128.89, 127.77, 126.78, 80.27, 47.45, 49.98. Anal. calcd. for $C_{24}H_{17}FN_4OS$; C, 67.28; N, 13.08; S, 7.47%. Found C, 67.08; N, 12.94; S, 7.08%; MS: *m/z* 428 $[M]^+$.

*3-(4-Methoxybenzylidene)-6,6-diphenyl-3,3a-dihydro-2H-imidazo[2,1-b]pyrazol[3,4-d][1,3] thiazol-7(6H)-one (**5d**)*

Yield 80%, m.p. 228°C; IR (KBr) cm^{-1}. 3271 (N–H str.) 3047 (C–H Ar–H), 1731 (C=O), 1532 (C=N), 1103 (C–O); ^{1}H NMR (DMSO d_6) δ: 6.7–7.1 (m, 14H, Ar–H), 6.62 (s, 1H, NH), 4.54 (d, 1H, –CH–Ar), 3.38 (d, 1H, –CH–S), 3.60 (3H, s, OCH_3); ^{13}C-NMR (DMSO d_6) δ: 173.34, 154.23, 164.02, 143.88, 140.46,139.27, 132.17, 130.37, 128.67, 129.18, 127.78, 126.78, 79.12, 55.95, 47.65, 49.37. Anal. calcd. for $C_{25}H_{20}N_4O_2S$; C, 68.18; N, 12.72; S, 7.27%. Found C, 67.80; N, 12.34; S, 6.87%; MS: *m/z* 440 $[M]^+$.

*3-(4-N,N-Dimethylbenzylidene)-6,6-diphenyl-3, 3a-dihydro-2H-imidazo[2,1-b]pyrazolo[3,4-d] [1,3]thiazol-7(6H)-one (**5e**)*

Yield 79%, m.p. 219°C; IR (KBr) cm^{-1} 3268 (N–H str.) 3039 (C–H, Ar–H), 1724 (C=O), 1562 (C=N); ^{1}H NMR

(DMSO d_6) δ: 6.9–7.4 (m, 14H, Ar–H), 6.52 (s, 1H, NH), 4.32 (d, 1H, –CH–Ar), 3.45 (d, 1H, –CH–S), 3.12 (6H, s, $N(CH_3)_2$; ^{13}C-NMR (DMSO d_6) δ:173.23, 154.56, 164.72, 143.64, 140.26,139.12, 132.11, 130.43, 128.54, 129.58, 127.78, 126.17, 79.34, 55.65, 47.87, 49.37, 42.76. Anal. calcd. for $C_{26}H_{23}N_5OS$; C, 68.87; N, 15.45; S, 7.06%. Found C, 68.56; N, 15.23; S, 6.78%; MS: *m/z* 453 $[M]^+$.

*Synthesis of 2-N-ethoxyphthalimido 3-(4-chlorophenyl)-6, 6-diphenyl-3,3a-dihydro-2H-imidazo [2,1-b]pyrazolo[3,4-d][1,3]thiazol-7(6H)-one (**7a**)*

A mixture of 5a (0.01 mol) and bromoalkoxyphthalimide (0.01 mol) in absolute ethanol (15 ml) was refluxed for 16 h. using pyridine (0.02 mol) as a base. It was concentrate by removing the solvent under reduced pressure and the resultant filtrate was poured into crushed ice to obtain solid product, which was filtered, dried and recrystallized from alcohol.

Yield 77%, m.p. 194°C; IR (KBr) cm^{-1}: 3032 (C–H, Ar–H), 2963 (C–H, CH_2 str.), 1726, 1705 (C=O), 1527 (C=N), 1492 (N–O), 1013 (C–O), 747 (C–Cl); ^{1}H NMR (DMSO d_6) δ: 7.3–7.9 (m, 18H, Ar–H), 4.44 (t, 2H, OCH_2, $J = 6.0$), 3.75 (t, 2H, NCH_2, $J = 5.7$), 4.29 (d, 1H, –CH–Ar), 3.34 (d, 1H, –CH–S); ^{13}C-NMR (DMSO d_6) δ: 172.84, 162.45, 161.60, 155.36, 142.80, 135.10, 132.15, 130.0, 129.70, 129.10, 128.90, 128.20, 126.03, 79.80, 65.80, 52.40, 49.12, 45.30. Anal. calcd. for $C_{34}H_{24}ClN_5O_4S$; C, 64.45; N, 11.04; S, 5.03%. Found C, 64.16; N, 10.50; S, 4.85%; MS: *m/z* 633 $[M]^+$, 635 $[M + 2]^+$.

Compounds (**7b–e**) were prepared in similar way with minor changes in reflux time. Their spectral data are given below:

*2-N-ethoxyphthalimido-3,6,6-triphenyl-3,3a-dihydro-2H-imidazo[2,1-b]pyrazolo[3,4-d][1,3] thiazol-7(6H)-one (**7b**)*

Yield 74%, m.p. 187°C; IR (KBr) cm^{-1}: 3028 (C–H, Ar–H), 2953 (C–H, CH_2), 1720,1702 (C=O), 1523 (C=N), 1490 (N–O), 1019 (C–O); ^{1}H NMR (DMSO d_6) δ: 7.0–7.7 (m, 18H, Ar–H), 4.34 (t, 2H, OCH_2, $J = 5.9$), 3.72 (t, 2H, NCH_2, $J = 5.6$), 4.23 (d, 1H, –CH–Ar), 3.30 (d, 1H, –CH–S); ^{13}C-NMR (DMSO d_6) δ:171.34, 162.56, 161.20, 155.65, 141.98, 135.36, 131.45, 129.90, 129.20, 129.08, 128.25, 128.12, 125.80, 78.85, 64.72, 51.20. 48.92, 44.94. Anal. calcd. for $C_{34}H_{25}N_5O_4S$; C, 68.11; N, 11.68; S, 5.34%. Found C, 67.60; N, 11.30; S, 5.05%; MS: *m/z* 599 $[M]^+$.

*2-N-ethoxyphthalimido-3-(4-fluorophenyl)-6,6-diphenyl-3, 3a-dihydro-2H-imidazo[2,1-b]pyrazolo[3,4-d] [1,3]thiazol-7(6H)-one (**7c**)*

Yield 78%, m.p. 198°C; IR (KBr) cm^{-1}: 3048 (C–H, Ar–H), 2967 (C–H, CH_2), 1732,1710 (C=O), 1554 (C=N), 1498 (N–O), 1018 (C–O),1185 (C–Cl); ^{1}H NMR (DMSO d_6) δ: 7.2–7.8 (m, 18H, Ar–H), 4.47 (t, 2H, OCH_2, $J = 6.1$), 3.77 (t, 2H, NCH_2, $J = 5.8$), 4.28 (d, 1H, –CH–Ar), 3.36 (d, 1H, –CH–S); ^{13}C-NMR (DMSO d_6) δ:172.86, 163.16, 161.50, 155.90, 141.96, 136.16, 131.95, 129.96, 129.42, 129.68, 128.75, 128.43, 125.87, 79.45, 65.46, 51.87, 49.19, 45.15, Anal. calcd. for $C_{34}H_{24}FN_5O_4S$; C, 66.12; N, 11.34; S, 5.18%. Found C, 65. 70; N, 11.21; S, 4.96%; MS: *m/z* 617 $[M]^+$.

*2-N-ethoxyphthalimido-3-(4-methoxybenzylidene)-6, 6-diphenyl-3,3a-dihydro-2H-imidazo[2,1-b]pyrazolo [3,4-d][1,3]thiazol-7(6H)-one (**7d**)*

Yield 75%, m.p. 184°C; IR (KBr) cm^{-1}: 3042 (C–H, Ar–H), 2964 (C–H, CH_2), 1727,1711 (C=O), 1544 (C=N), 1487 (N–O), 1016 (C–O); ^{1}H NMR (DMSO d_6) δ: 6.8–7.3 (m, 18H, Ar–H), 4.38 (t, 2H, OCH_2, $J = 5.9$), 3.72 (t, 2H, NCH_2, $J = 5.7$), 4.21 (d, 1H, –CH–Ar), 3.29 (d, 1H, –CH–S), 3.34 (3H, s, OCH_3); ^{13}C-NMR (DMSO d_6) δ:172.45, 163.29, 161.48, 155.50, 141.76, 137.06, 132.15, 129.86, 129.65, 129.52, 128.23, 128.65, 125.67, 79.21, 65.53, 51.62. 49.34, 46.25. Anal. calcd. for $C_{35}H_{27}N_5O_5S$; C, 66.77; N, 11.12; S, 5.08%. Found C, 66. 25; N, 11.05; S, 4.76%; MS: *m/z* 629 $[M]^+$.

*2-N-ethoxyphthalimido-3-(4-N,N-dimethylbenzylidene)-6, 6-diphenyl-3,3a-dihydro-2H-imidazo [2,1-b] pyrazolo[3,4-d][1,3]thiazol-7(6H)-one (**7e**)*

Yield 76%, m.p. 191°C; IR (KBr) cm^{-1}: 3040 (C–H, Ar–H), 2958 (C–H,CH_2), 1724, 1698 (C=O), 1547 (C=N), 1482 (N–O), 1021 (C–O); ^{1}H NMR (DMSO d_6) δ: 6.7–7.2 (m, 18H, Ar–H), 4.34 (t, 2H, OCH_2, J = 5.8), 3.67 (t, 2H, NCH_2, $J = 5.5$), 4.18 (d, 1H, –CH–Ar), 3.23 (d, 1H, −CH−S), 3.25 (6H, s, $N(CH_3)_2$; ^{13}C-NMR (DMSO d_6) δ:172.76, 163.23, 161.94, 155.80, 141.12, 137.34, 132.46, 129.26, 129.75, 129.78, 128.45, 128.25, 125.10, 78.89, 65.43, 51.41. 49.20, 46.55. Anal. calcd. for $C_{36}H_{30}N_6O_4S$; C, 67.28; N, 13.08; S, 4.98%. Found C, 67. 15; N, 12.90; S, 4.50%; MS: *m/z* 642 $[M]^+$.

*Synthesis of 2-amino-4-(4-chlorophenyl)-7, 7diphenylimidazo[2′,1′:2,3][1,3]thiazolo[4,5-d] pyrimidin-8(7H)-one (**8a**)*

A mixture of compound **4a** (0.01 mol) and guanidine nitrate (0.01 mol) in absolute alcohol was refluxed. An aqueous solution of NaOH (40%, 5 ml) was added to it portion-wise during 3 h. The heating was continued for the next 8 h. The reaction mixture was cooled and poured into crushed ice. The yellow-coloured solid separate was filtered, dried and recrystallized from absolute alcohol. Yield

72%, m.p. >300°C; IR (KBr) cm^{-1}: 3212, 3357 (N–H, 2H, NH_2), 3032 (C–H, Ar–H), 1657 (C=O), 1489 (C=N), 1384 (C–N), 748 (C–Cl); ^{1}H NMR (DMSO d_6) δ: 6.8–7.4 (m, 18H, Ar–H), 6.74 (s, 2H, NH_2); ^{13}C-NMR (DMSO d_6) δ: 167.34, 164.78, 163.05, 152.80, 151.22, 142.85, 134.10, 133.32, 129.46, 129.04, 128.86, 128.10, 127.15, 125.50, 78.60. Anal. calcd. for $C_{25}H_{16}ClN_5OS$; C, 63.96; N, 14.92; S, 6.79%. Found C, 63.40; N, 14.58; S, 6.45%; MS: *m/z* 469 $[M]^+$, 471 $[M + 2]^+$.

Similarly, other compound (**8b–e**) was also synthesized and its characteristic data are given below:

*2-Amino-4,7,7-triphenylimidazo[2′,1′:2,3][1,3]thiazolo [4,5-d]pyrimidin-8(7H)-one (**8b**)*

Yield 71%, m.p. 289°C; IR (KBr) cm^{-1}: 3208, 3345 (N–H, 2H, NH_2), 3028 (C–H, Ar–H), 1653 (C=O), 1485 (C=N), 1382 (C–N); ^{1}H NMR (DMSO d_6) δ: 6.4–7.1 (m, 18H, Ar–H), 6.72 (s, 2H, NH_2); ^{13}C-NMR (DMSO d_6) δ: 167.17, 164.34, 163.25, 152.56, 151.31, 142.75, 134.34, 133.12, 129.43, 129.54, 128.76, 128.24, 127.46, 125.67, 78.32 Anal. calcd. for $C_{25}H_{17}N_5OS$; C, 68.96; N, 16.09; S, 7.35% Found C, 68.76; N, 15.98; S, 7.02%; MS: *m/z* 435 $[M]^+$.

*2-Amino-4-(4-fluorophenyl)-7,7diphenylimidazo[2′,1′:2,3] [1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one (**8c**)*

Yield 76%, m.p. >300°C; IR (KBr) cm^{-1}: 3226,3364 (N–H, 2H, NH_2), 3047 (C–H, Ar–H), 1664 (C=O), 1496 (C=N), 1389 (C–N), 1178 (C–F); ^{1}H NMR (DMSO d_6) 7.2–7.8 (m, 18H, Ar–H), 6.83 (s, 2H, NH_2); ^{13}C-NMR (DMSO d_6) δ: 166.87, 164.56, 163.78, 152.77, 151.68, 142.87, 134.74, 133.54, 130.12, 129.68, 128.77, 128.64, 127.87, 125.98, 78.56. Anal. calcd. for $C_{25}H_{16}FN_5OS$; C, 66.22; N, 15.45; S, 7.06%. Found C, 66.00; N, 15.08; S, 6.68%; MS: *m/z* 453 $[M]^+$.

*2-Amino-4-(4-methoxybenzylidene)-7,7diphenylimidazo [2′,1′:2,3][1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one (**8d**)*

Yield 73%, m.p. 292°C; IR (KBr) cm^{-1}: 3207,3342 (NH, 2H, NH_2), 3034 (C–H, Ar–H), 1674 (C=O), 1488 (C=N), 1384 (C–N), 1012 (C–O); ^{1}H NMR (DMSO d_6) 6.5–6.9 (m, 18H, Ar–H), 6.78 (s, 2H, NH_2), 3.12 (3H, s, OCH_3); ^{13}C-NMR (DMSO d_6) δ: 166.74, 164.46, 163.83, 152.63, 151.45, 142.67, 134.13, 133.17, 130.46, 129.79, 128.84, 128.94, 127.56, 125.18, 78.34. Anal. calcd. for $C_{26}H_{19}N_5O_2S$; C, 67.09; N, 15.05; S, 6.88%. Found C, 66.96; N, 14.80; S, 6.54%; MS: *m/z* 465 $[M]^+$.

*2-Amino-4-(4-N,N-dimethylbenzylidene)-7, 7diphenylimidazo[2′,1′:2,3][1,3]thiazolo[4,5-d] pyrimidin-8(7H)-one (**8e**)*

Yield 70%, m.p. 286°C; IR (KBr) cm^{-1}: 3213–3332 (N–H, 2H, NH_2), 3031 (C–H, Ar–H), 1670 (C=O), 1482 (C=N), 1380 (C–N), 1016 (C–O); ^{1}H NMR (DMSO d_6) δ: 6.7–7.1 (m, 18H, Ar–H), 6.72 (s, 2H, NH_2), 3.12 (6H, s, $N(CH_3)_2$; ^{13}C-NMR (DMSO d_6) δ: 166.37, 164.75, 163.13, 152.87, 151.45, 142.56, 134.23, 133.76, 130.34, 129.54, 128.34, 128.67, 127.16, 125.28, 78.37. Anal. calcd. for $C_{27}H_{22}N_6OS$; C, 67.78; N, 17.57; S, 6.69%. Found C, 66.41; N, 17.20; S, 6.42%; MS: *m/z* 478 $[M]^+$.

*Synthesis of 4-(4-chlorophenyl)-2-(N-ethoxyphthalimido amino)-7,7-diphenylimidazo[2′,1′:2,3] [1,3]thiazolo [4,5-d]pyrimidin-8(7H)-one (**9a**)*

Compound **8a** (0.01 mol) was refluxed in dry acetone (20 ml) containing K_2CO_3 (0.01 mol) as base and bromoalkoxyphthalimide 6 (0.01 mol) for 16–20 h. Excess of solvent was removed under reduced pressure. The separated solid was filtered, washed and recrystallized from ethanol. Yield 70%, m.p. 124°C; IR (KBr) cm^{-1}: 3360 (N–H, str), 3042 (C–H, Ar–H), 2947 (C–H, CH_2), 1722, 1708 (C=O), 1565 (C=N), 1490 (N–O), 762 (C–Cl); ^{1}H NMR (DMSO d_6) δ: 6.6–7.8 (m, 18H, Ar–H), 7.07 (s, 1H, N–H), 4.44 (t, 2H, OCH_2, $J = 6.0$), 3.75 (t, 2H, NCH_2, $J = 5.7$); ^{13}C-NMR (DMSO d_6) δ: 175.17, 175.79, 155.96, 139.90, 138.34, 128.75, 128.49, 128.42, 128.01, 126.56, 72.94, 70.19, 40.35, 40.07, 39.79, 39.51, 39.24, 38.96, 38.68. Anal. calcd. for $C_{35}H_{23}ClN_6O4S$; C, 63.63; N, 12.72; S, 4.86%. Found C, 63.16; N, 12.45; S, 4.35%; MS: *m/z* 660 $[M]^+$, 662 $[M + 2]^+$.

Compounds (**9b–e**) were synthesized in similar way with alteration in reflux time. Their spectral data are given below:

*2-(N-ethoxyphthalimidoamino)-4,7,7-triphenylimidazo [2′,1′:2,3][1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one (**9b**)*

Yield 69%, m.p. 119°C; IR (KBr) cm^{-1}: 3358 (N–H, str), 3040 (C–H, Ar–H), 2937 (C–H, CH_2), 1719, 1703 (C=O), 1559 (C=N), 1487 (N–O); ^{1}H NMR (DMSO d_6) δ: 6.2–6.8 (m, 18H, Ar–H), 7.02 (s, 1H, N–H), 4.40 (t, 2H, OCH_2, $J = 5.9$), 3.73 (t, 2H, NCH_2, $J = 5.7$); ^{13}C-NMR (DMSO d_6) δ: 168.10, 165.67, 163.45, 161.78, 153.23, 142.45, 134.67, 133.13, 132.45, 131.89, 129.56, 128.45, 128.67, 128.23, 128.19, 127.35, 125.34, 79.67, 70.90, 49.96. Anal. calcd. for $C_{35}H_{24}N_6O_4S$; C, 67.30; N, 13.46; S, 5.12%. Found *C*, 67.19; *N*, 13.21; *S*, 4.87%; MS: *m/z* 624 $[M]^+$.

*4-(4-Fluorophenyl)-2-(N-ethoxyphthalimido amino)-7, 7-diphenylimidazo[2′,1′:2,3][1,3]thiazolo [4,5-d]pyrimidin-8(7H)-one (**9c**)*

Yield 74%, m.p. 136°C; IR (KBr) cm^{-1}: 3367 (N–H, str), 3047 (C–H, Ar–H), 2956 (C–H, CH_2), 1727,1714 (C=O), 1568 (C=N), 1496 (N–O),1176 (C–F); ^{1}H NMR (DMSO d_6) δ: 6.7–7.4 (m, 18H, Ar–H), 7.13 (s, 1H, N–H), 4.48 (t, 2H, OCH_2, $J = 6.0$), 3.78 (t, 2H, NCH_2, $J = 5.9$); ^{13}C-NMR (DMSO d_6) δ: 168.46, 165.54, 163.32, 161.45, 153.23, 142.34, 134.12, 133.26, 132.34, 131.67, 129.36, 128.25, 128.33, 128.87, 128.99, 127.12, 125.45, 79.34, 70.98, 50.23. Anal. calcd. for $C_{35}H_{23}FN_6O_4S$; C, 65.42; N, 13.08; S, 4.98%. Found C, 65.06; N, 12.60; S, 4.36%. MS: *m/z* 642 $[M]^+$.

*4-(4-Methoxybenzylidene)-2-(N-ethoxyphthalimido amino)7,7-diphenylimidazo[2′,1′:2,3][1,3] thiazolo[4,5-d]pyrimidin-8(7H)-one (**9d**)*

Yield 71%, m.p. 121°C; IR (KBr) cm^{-1}: 3362 (N–H, str), 3043 (C–H, Ar–H), 2942 (C–H, CH_2), 1722, 1711 (C=O), 1548 (C=N), 1487 (N–O), 1018 (C–O); ^{1}H NMR (DMSO d_6) δ: 6.4–6.8 (m, 18H, Ar–H), 7.07 (s, 1H, N–H), 4.34 (t, 2H, OCH_2, $J = 5.7$), 3.68 (t, 2H, NCH_2, $J = 5.6$), 3.24 (s, 3H, OCH_3); ^{13}C-NMR (DMSO d_6) δ: 168.34, 164.23, 163.65, 161.63, 153.87, 142.35, 134.10, 133.32, 132.65, 131.42, 129.76, 129.41, 128.93, 128.43, 127.99, 127.36, 125.23, 79.45, 70.56, 50.12. Anal. calcd. for $C_{36}H_{26}N_6O_5S$; C, 66.05; N, 12.84; S, 4.89%. Found C, 65.96; N, 12.60; S, 4.46%; MS: *m/z* 654 $[M]^+$.

*4-(4-N,N-dimethylbenzylidene)-2-(N-ethoxyphthalimi-doamino)-7,7-diphenylimidazo[2′,1′:2,3] [1,3]thiazolo[4,5-d]pyrimidin-8(7H)-one (**9e**)*

Yield 69%, m.p. 137°C; IR (KBr) cm^{-1}: 3356 (N–H, str), 3034 (C–H, Ar–H), 2940 (C–H, CH_2), 1719, 1710 (C=O), 1543 (C=N), 1489 (N–O); ^{1}H NMR (DMSO d_6) δ: 6.3–6.7 (m, 8H, Ar–H), 7.10 (s, 1H, N–H), 4.30 (t, 2H, OCH_2, $J = 5.9$), 3.64 (t, 2H, NCH_2, $J = 5.8$), 3.26 (s, 6H, $N(CH_3)_2$; ^{13}C-NMR (DMSO d_6) δ: 167.23, 164.45, 162.95, 161.33, 152.54, 143.45, 134.67, 133.12, 132.32, 131.67, 130.16, 129.14, 128.45, 128.78, 128.19, 127.76, 124.33, 80.41, 70.34, 50.56. Anal. calcd. for $C_{37}H_{29}N_7O_4S$; C, 66.56; N, 14.69; S, 4.79%. Found C, 66.10; N, 14.31; S, 4.16%; MS: *m/z* 667 $[M]^+$.

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