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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anticonvulsant activities of functionalized 5-(isoindole-1,3-dione)-pyrimidinones

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Abstract The present work involves the synthesis of previously unknown 5-(isoindole-1,3-dione) pyrimidinones by [4 + 2] cycloaddition reactions of functionalized 1,3-diazabuta-1,3-dienes with phthalimidoketene, generated in situ from phthaloylglycine, tosyl chloride, and triethylamine. The 5-(isoindole-1,3-dione)-pyrimidinones have been screened in vivo for their anticonvulsant activities using MES and PTZ methods. A comparative study for in vivo anticonvulsant activities of these functionalized pyrimidinones with a variety of substitutions at different positions was also conducted. 2-(4-Dimethylamino-6-oxo-1,2-diphenyl-1,6-dihydro-pyrimidin-5-yl)-isoindole-1,3-dione has shown the maximum anticonvulsant activities at 100 mg/kg test dose using MES and PTZ tests.

Keywords Cycloadditions · 1,3-Diazabuta-1,3-dienes · 5-(Isoindole-1,3-dione)-pyrimidinones · Anticonvulsant activities · MES test · *sc*PTZ test

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Introduction

Functionalized pyrimidinones are an important class of molecules with diverse pharmacological profiles (Brown, 1984). Pyrimidinones substituted at either C-5 or C-6 positions have shown the diverse biological activities (Knapp, 1995). C-6-substituted uracil 1-[(2 hydroxyethyl) methyl]-6-(phenylthio) thymine (HEPT) (Giles, 2002) and its analogues, and emivirine (EMV) have shown the inhibition of HIV-1 reverse transcriptase (Hopkins *et al*., 1999). Acyclovir is in clinical use, and Cidofovir, (*S*)-3-hydroxy-2-phosphonomethoxypropyl cytosine, possesses broad-spectrum activity against a variety of DNA viruses (Tanaka *et al*., 1992; Zakharova *et al*., 2011). The C-5/C-6-substituted pyrimidinones have been reported to possess antitubercular, antitumor, antipsychotic as well as antibiotic, antifungal (Petricci *et al*., 2006; Edrees *et al*., 2010; Brands *et al*., 2003; Fu *et al*., 2005) activities. Thus, the literature survey clearly reveals that appropriate functionalities at different positions of pyrimidinones are crucial in deciding the pharmacological profile of pyrimidinones. The most useful method for the preparation of functionalized pyrimidinones involves the cycloaddition reactions of 1,3-diazabuta-1,3-dienes with different heterocumulenes (Jayakumar *et al*., 2002). Of these, ketene has extensively utilized for the synthesis of functionalized pyrimidinones with different 1,3-diazabuta-1,3-dienes (Jayakumar *et al*., 2002).

On the other hand, epilepsy is a growing health problem in large section of world population. About 30 % patients with epilepsy have developed resistance to all available antiepileptic drugs (AEDs). Moreover, these AEDs are associated with various side effects. Hence, there is an unmet need to discover novel antiepileptic drugs with improved efficacy and safety (Loscher and Schmidt, 2011).

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Recently, the literature reports have revealed in vivo anticonvulsant activities of novel heterocyclic synthons, viz. dihydropyridines (Ulloora *et al*., 2013a, b), imidazo-[1,2-a] pyridine (Ulloora *et al*., 2013a, b) using standard PTZ and MES tests. As a part of our ongoing interest to find novel psychoactive compounds, it was thought worthwhile to evaluate the anticonvulsant activities of functionalized pyrimidinones **3a–h** synthesized by [4 + 2] cycloaddition reactions of differently substituted 1,3-diaza-1,3-butadienes **1a–h** with phthalimidoketene. The phthalimidoketene was generated in situ from the phthaloylglycine using *p*-toluene sulphonylchloride and triethylamine in dry chloroform at room temperature.

Materials and methods

Unless otherwise noted, commercially available materials were used without further purification. Thin-layer chromatography (TLC) was carried out using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds visualized in UV. NMR spectra were recorded on a Bruker 300 MHz spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts (δ) are quoted in parts per million (ppm) relative to internal solvent reference ($CDCl_3$ $\delta = 7.26$ for ^{1}H NMR and $\delta = 77.0$ for ^{13}C NMR). Coupling constants are given in Hz, and chemical shifts are reported in δ values in ppm. Data are reported as followed: chemical shift, multiplicity (s = singlet, s br = broad singlet, d = doublet, t = triplet, dd = double doublet, and dt = double triplet, m = multiplet), coupling constants (Hz), and integration. High-resolution mass spectra were recorded on a Bruker-microTOF-Q II mass spectrometer. Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer.

General procedure for the preparation of 5-isoindole-1,3-dione pyrimidinones pyrimidinones, **(3a–h)** To a solution of 1,3-diazabutadiene **1a–h** (5 g, 1 eq.), phthaloylglycine **2** (1.5 eq.), and triethylamine (4 eq.) in dry chloroform (100 mL) at 0 °C was added dropwise a solution of *p*-TsCl (2.0 eq.) in dry chloroform. The progress of the reaction was monitored with the help of TLC. After completion of reaction, a usual workup was performed using chloroform and brine solution. The organic layers were collected, dried over sodium sulfate, and evaporated to get crude product. The crude product was recrystallized using 10 % chloroform in diethyl ether to get pure 5-isoindole-1,3-dione pyrimidinones (**3a–h**) in good yields.

2-(4-Diethylamino-6-oxo-1,2-diphenyl-1,6-dihydro-pyrimidin-5-yl)-isoindole-1,3-dione, **3a** Yield 75 %; m.pt 185–187 °C; IR (KBr) υ 1662 cm^{-1}; ^{1}H NMR (300 MHz) in $CDCl_3$; δ 1.23 (m, 6H, –CH_3),δ 3.44 (m, 4H, 2x–CH_2–), δ 7.23 (m, 10H, H-aromatic);7.92 (m, 4H, H-aromatic), ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.25, 44.83, 99.16, 124.38, 124.39, 127.30, 128.17, 129.83, 132.75, 132.75, 134.30, 135.2, 135.09, 147.38, 154.2, 157.1, 160.12, 166.21; m/z 465$(M + 1)^+$. HRMS calcd for $C_{28}H_{25}N_4O_3$ $(M)^+$: 465.1927, found 465.1930.

2-(4-Dipropylamino-6-oxo-1,2-diphenyl-1,6-dihydro-pyrimidin-5-yl)-isoindole-1,3-dione, **3b** Yield 68 %; m.pt 154–155 °C; IR (KBr) υ 1665 cm^{-1}; ^{1}H NMR (300 MHz) in $CDCl_3$, δ 0.74 (m, 6H, –CH_3), δ 1.69 (m, 4H, 2x–CH_2–), δ 3.43 (m, 4H, CH_2–N–CH_2), δ 7.19 (m, 10H, H-aromatic); δ 7.36 (2H, H-aromatic), δ 7.92 (m, 2H, H-aromatic) ^{13}C NMR (75.5 MHz, $CDCl_3$) in $CDCl_3$: 11.24, 21.91, 52.05, 91.79, 123.70, 127.82, 128.16, 128.63, 129.06, 129.27, 129.70,132.28, 134.31, 134.96, 137.25, 156.09, 157.62, 160.90, 169.46, m/z 493 $(M + 1)^+$. HRMS calcd for $C_{30}H_{29}N_4O_3$ $(M + 1)^+$: 493.2240, found 493.2243.

2-(4-Morpholin-4-yl-6-oxo-1,2-diphenyl-1,6-dihydro-pyrimidin-5-yl)-isoindole-1,3-dione, **3c** Yield 78 %; m.pt 161–164 °C; IR (KBr) υ 1671 cm^{-1}; ^{1}H NMR (300 MHz) in $CDCl_3$ δ 3.62 (m, 4H, –CH_2–N–CH_2–), δ 3.81 (m, 4H, CH_2–O–CH_2–), δ 7.19 (m, 10H, H-aromatic); δ 7.75 (m, 2H, H-aromatic), 7.93 (m, 2H, H-aromatic), ^{13}C NMR (75.5 MHz, $CDCl_3$) in $CDCl_3$: δ 49.8, 66.2, 98.21, 124.24, 128.59, 128.75, 128.91, 128.97, 129.01, 129.10, 129.78, 132.14, 134.87, 134.9, 137.8, 157.1, 160.1, 168.2; m/z 493 $(M + 1)^+$, HRMS calcd for $C_{28}H_{23}N_4O_4$ $(M + 1)^+$: 479.1719, found 479.1721.

2-(6-Oxo-1,2-diphenyl-4-pyrrolidin-1-yl-1,6-dihydro-pyrimidin-5-yl)-isoindole-1,3-dione, **3d** Yield 80 %; m.pt 255–256 °C; IR (KBr) υ 1720, 1655 cm^{-1}; ^{1}H NMR (300 MHz) in $CDCl_3$ δ 1.89 (m, 4H, 2x–CH_2–), δ 3.52 (m, 4H, (–CH_2–N–CH_2–), δ 7.27 (m, 10H, H-aromatic), 7.74 (m, 2H, H-aromatic), 7.93 (2H, H-aromatic); ^{13}C NMR (75.5 MHz, $CDCl_3$) in $CDCl_3$: δ 25.29, 48.29, 124.06, 128.40, 128.87, 129.37, 129.54, 129.96, 132.72, 134.46, 135.26, 137.50, 156.94, 160.85, 169.63; m/z 463 $(M + 1)^+$ HRMS calcd for $C_{28}H_{23}N_4O_3$ $(M + 1)^+$: 463.1770, found 463.1772.

2-(6-Oxo-1,2-diphenyl-4-piperidin-1-yl-1,6-dihydro-pyrimidin-5-yl)-isoindole-1,3-dione **3e** Yield 83 %; m.pt 195–197 °C; IR (KBr) υ 1658 cm^{-1}; ^{1}H NMR (300 MHz) in $CDCl_3$; δ 1.29 (m, 6H, –CH_2–CH_2–CH_2), δ 3.69 (m, 4H, CH_2–N–CH_2), 7.26 (m, 10H, H-aromatic); 7.71 (m, 2H, H-aromatic), 7.98 (m, 2H, H-aromatic), ^{13}C NMR (75.5 MHz, $CDCl_3$) in $CDCl_3$: δ 26.11, 47.56, 92.69, 123.74, 127.6, 128.2, 128.5, 128.6, 129.03, 129.27, 129.75, 132.33, 134.28, 134.83, 137.19, 156.5, 158.0, 160.9, 168.59; m/z 477 $(M + 1)^+$ HRMS calcd for $C_{29}H_{25}N_4O_3$ $(M + 1)^+$: 477.1927, found 477.1930.

2-(6-Oxo-2-phenyl-4-piperidin-1-yl-1-p-tolyl-1,6-dihydro-pyrimidin-5-yl)-isoindole-1,3-dione, **3f** Yield 88 %; m.pt 210–212 °C; IR (KBr) υ 1652 cm^{-1}; ^1H NMR (300 MHz) in $CDCl_3$; δ 1.30 (m, 6H, $–CH_2–CH_2–CH_2$), 2.45 (3H, $–CH_3$) δ 3.55 (m, 4H, $–CH_2–N–CH_2–$), δ 7.25 (m, 9H, H-aromatic); δ 7.74 (m, 2H, H-aromatic), δ 7.93 (2H, H-aromatic), ^{13}C NMR (75.5 MHz, $CDCl_3$) in $CDCl_3$: δ 21.2, 26.45, 48.53, 95.69, 123.11, 127.5, 127.92, 128.41, 128.72, 129.24, 129.47, 129.56, 131.1, 134.21, 134.5, 137.18, 157.4, 158.28, 161.7, 168.2, 94.12, 124.3, 128.24, 128.5, 128.97, 129.12, 129.34, 129.41, 129.79, 132.24, 135.3, 135.1, 137.7, 157.83, 160.2, 168.23, m/z 491 $(M + 1)^+$ HRMS calcd for $C_{30}H_{27}N_4O_3$ $(M + 1)^+$: 491.2083, found 491.2085.

2-(6-Oxo-2-phenyl-4-pyrrolidin-1-yl-1-p-tolyl-1,6-dihydro-pyrimidin-5-yl)-isoindole-1,3-dione, **3g** Yield 85 %; m.pt 241–244 °C; IR (KBr) υ 1660 cm^{-1}; ^1H NMR (300 MHz) in $CDCl_3$; δ 1.87 (m, 4H, $–CH_2–CH_2–$), δ 2.43 (3H, $–CH_3$), δ 3.57 (m, 4H, $–CH_2–N–CH_2$), δ 7.32 (m, 9H, H-aromatic); δ 7.77 (m, 2H, H-aromatic), δ 7.97 (2H, H-aromatic) ^{13}C NMR (75.5 MHz, $CDCl_3$) in $CDCl_3$: δ 20.3, 25.8, 49.2, 94.12, 124.3, 128.24, 128.5, 128.97, 129.12, 129.34, 129.41, 129.79, 132.24, 135.3, 135.1, 137.7, 157.83, 160.2, 168.23, m/z 491 $(M + 1)^+$ HRMS calcd for $C_{29}H_{25}N_4O_3$ $(M + 1)^+$: 477.1927, found 477.1930.

2-(4-Dimethylamino-6-oxo-1,2-diphenyl-1,6-dihydro-pyrimidin-5-yl)-isoindole-1,3-dione, **3h** Yield 63 %; m.pt 135–136 °C; IR (KBr) υ 1658 cm^{-1}; ^1H NMR (300 MHz) in $CDCl_3$; δ 3.17 (m, 6H, $–CH_3$), 7.29 (m, 10H, H-aromatic); 7.78 (m, 2H, H-aromatic), 7.95 (m, 2H, H-aromatic), ^{13}C NMR (75.5 MHz, $CDCl_3$) in $CDCl_3$: δ 45.99, 123.74, 125.97, 127.80, 128.17, 128.61, 128.63, 129.05, 129.25, 129.71, 132.44, 134.15, 134.99, 137.20, 156.50, 158.60, 160.72, 168.96; m/z 437 $(M + 1)^+$ HRMS calcd for $C_{26}H_{21}N_4O_3$ $(M + 1)^+$: 437.1614, found 437.1616.

Result and discussion

Chemistry

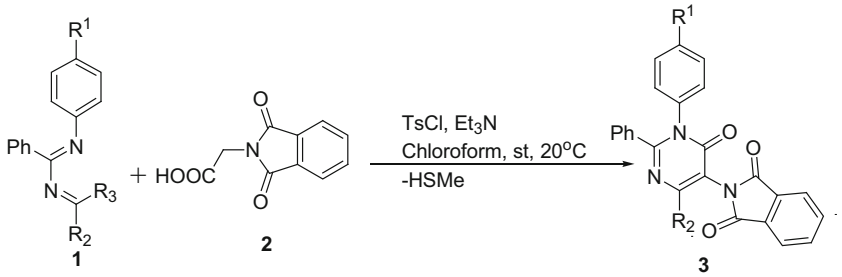
The starting materials 1,3-diazabuta-1,3-dienes (**1a–h**) used in the synthesis of desired substrates were prepared by reported methods (Sharma and Mahajan, 1997). Phthaloylglycine (**2**) was prepared by the condensation of phthalic anhydride and glycine on oil bath for thirty minutes at 200 °C. We initially investigated the reaction of 1,3-diazabuta-1,3-dienes (**1a–h**) with ketene derived in situ from the phthaloylglycine using *p*-toluene sulphonylchloride and triethylamine at 0 °C. The reaction resulted in the formation of pyrimidinones **3a–h** in good yields. Best yields of the [4 + 2] cycloadducts were observed with the use of **1e** as diene. The reaction gave poor yield of cycloadducts when the reaction conducted at high temperature (50 °C using dichloroethane as solvent). The [4 + 2] cycloaddition also gave the poor yield of adducts when reaction conducted in nonpolar aprotic solvent, viz toluene and benzene. A plausible mechanism involves the initial [4 + 2] cycloaddition reactions of 1,3-diazabutadienes, followed by the elimination of the mercaptomethanol (Scheme 1).

The 2-(6-oxo-1,2-diaryl-4-secondary amino-1-yl-1,6-di hydro-pyrimidin-5-yl)-isoindole-1,3-diones, **3a–h**, were characterized with the help of analytical data and spectral evidences. The compound, **3e,** 2-(6-Oxo-1,2-diphenyl-4-piperidin-1-yl-1,6-dihydro-pyrimidin-5-yl)-isoindole-1,3-dione, for example, analyzed for $C_{29}H_{24}N_4O_3$ showed a (M + 1) peak at m/z 477 in its mass spectrum. Its IR spectrum showed strong absorption peaks at 1658 cm^{-1} corresponding to the carbonyl group of pyrimidinones. The ^1H NMR (300 MHz) spectrum showed a two multiplet at δ 1.29 and δ 3.69 corresponding to methylene proton of piperidine ring. The ^{13}C NMR has shown the presence of carbonyl carbons at δ 160.9 and δ 168.59 corresponding to pyrimidinone and isoindole rings, respectively. The ^{13}C NMR has also shown the presence of piperidine ring carbons at δ 26.11 and δ 47.56.

Pharmacology

The compounds were initially screened virtually for potential anticonvulsant activities using computer software prediction of activity spectra for substances (PASS). Computer software PASS theoretically predicts different possible biological activities of chemical entity. This software determines the predicted activity spectrum of a compound as probable activity (P*a*) and probable inactivity (P*i*). Prediction of this spectrum by PASS is based on SAR analysis of the training set containing more than 205,000 compounds, which correlates with more than 3750 kinds of biological activity (Poroikov *et al*., 2003) PASS predictions of the synthesized compound are described in Table 1. PASS prediction clearly predicted for anticonvulsant activities in the 5-(isoindole-1,3 dione) pyrimidinone (**3a–h).** The compounds were then screened in vivo for the anticonvulsant activities. The maximal electroshock (MES) and subcutaneous pentylenetetrazole (PTZ) screening methods of Swinyard *et al.* (1952) with slight modifications (Singh and Goel, 2009; Kaur and Goel, 2011; Goel et al., 2011) were used as animal model for in vivo screening for anticonvulsant studies. The compounds were screened at two different concentrations, i.e., 30 and 100 mg/kg. The tested compounds **(3a–h)** afforded significant protection against generalized tonic–clonic seizures and generalized absence seizures, respectively. Further, Rotarod method

Scheme 1 Reaction of 1,3-diazabutadienes **1a–h** with phthaloylglycine (**2**)



1a R^1=H, R^2=$C_2H_5NC_2H_5$, R_3= SMe,
1b, R^1=H, R^2=$C_3H_7NC_3H_7$, R_3= SMe
1c, R^1=H, R^2= Morpholine, R_3= SMe
1d R^1=H, R^2= Pyrrolidine, R_3= SMe
1e, R^1=H, R^2=Piperidine, R_3= SMe
1f, R^1=CH_3, R^2=Piperidine, R_3= SMe
1g, R^1=CH_3,R^2=Pyrrolidine, R_3= SMe
1h, R^1=H,R^2=dimethylamine , R_3=SMe

3a R^1=H, R^2=$C_2H_5NC_2H_5$ (75%)
3b, R^1=H, R^2=$C_3H_7NC_3H_7$ (68%)
3c, R^1=H, R^2= Morpholine (78%)
3d R^1=H, R^2= Pyrrolidine (80%)
3e, R^1=H, R^2=Piperidine (83%)
3f, R^1=CH_3, R^2=Piperidine (88%)
3g, R^1=CH_3,R^2=Pyrrolidine (85%)
3h, R^1=H,R^2=dimethylamine (63%)

Table 1 PASS prediction score of the 5-(isoindole-1,3 dione)-pyrimidinone bifunctional hybrids (**3a**–**h**)

S. no	Compound	Anticonvulsant activity	
		Pa	Pi
1	**3a**	0.686	0.013
2	**3b**	0.656	0.015
3	**3c**	0.639	0.017
4	**3d**	0.647	0.016
5	**3e**	0.616	0.020
6	**3f**	0.651	0.016
7	**3g**	0.622	0.019
8	**3h**	0.799	0.007

was also employed for detection of motor impairment of the tested compounds (Goel *et al*., 2011). These animal studies were performed in accordance with the ethical standards on animal experimentations.

The screening results of active target molecules are summarized in Fig. 1. The compound (**3h**) showed a dose-dependent anticonvulsant effect in PTZ- and MES-induced convulsion. The most significant effect was observed at a 100-mg/kg dose. The screening studies clearly revealed that 5-isoindole pyrimidinones have in vivo anticonvulsant activity in albino mice. The 5-(isoindole-1,3 dione) pyrimidinone (**3h**) with dimethyl amine substitution has shown maximum anticonvulsant activities (Fig. 1; **3h**). The 5-(isoindole-1,3 dione) pyrimidinone with bulky substitution at C-4 position comparatively has less anticonvulsant activities (Fig. 1; **3a–3g)**. There was comparatively increase in anticonvulsant activities with increase in dosage from 30 mg/kg to 100 mg/kg. Furthermore, the Rotarod method also predicted the absence of motor impairment and hence confirms the no neurotoxicity of tested compound even at higher dose. The presence of isoindole moiety at C-5 position of pyrimidinone is crucial for the anticonvulsant activity as 5-amino pyrimidinone did not provide any anticonvulsant activity in both PTZ- and MES-induced convulsion.

Conclusion

In conclusion, we have reported the synthesis of previously unknown 5-(isoindole-1,3 dione) pyrimidinones by [4 + 2] cycloaddition reactions of 1,3-diazabuta-1,3-dienes with

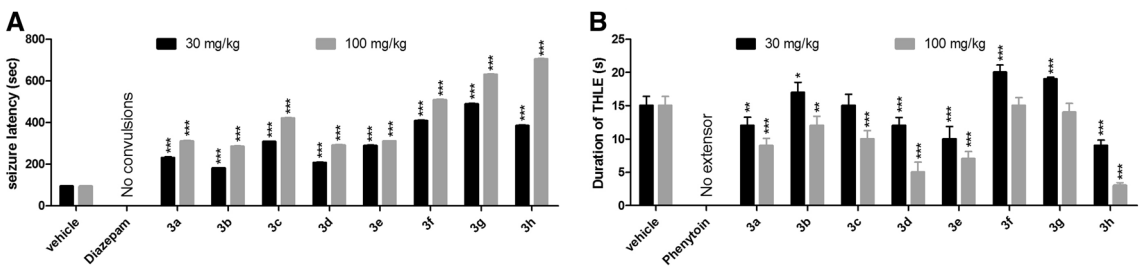


Fig. 1 Anticonvulsant activity of the 5-(isoindole-1,3 dione) pyrimidinones (**3a**–**h**) in **a** PTZ-induced convulsion and **b** MES-induced convulsion. All values are represented as mean ± SEM; $n = 6$, $^*p < 0.05$; $^{**}p < 0.01$ and $^{***}p < 0.001$ when compared to vehicle group. *THLE* tonic hindlimb extensor

phthlimidoketene. These pyrimidinones were tested in vivo for their anticonvulsant activities. The neurotoxicity studies also predicted the absence of neurotoxicity even at higher concentration of tested compounds. A compound with dimethylamine at C-4 position has shown the maximum anticonvulsant activity in both standard methodologies using PTZ and MES test. Further work on such functionalized isoindole pyrimidinone is in progress and will be reported in near future.

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