International Journal of Chemical Studies

P-ISSN2349–8528
E-ISSN 2321–4902
IJCS 2016; 4(1): 61-63

Received: 12-11-2015
Accepted: 13-12-2015

RS Dhivare
Department of Chemistry, J.J.T. University, Rajasthan, India

SS Rajput
Department of Chemistry, SVS's Dadasaheb Rawal College, Dondaicha, MS, India

R Yadav
Department of Chemistry, J.J.T. University, Rajasthan, India

Correspondence
RS Dhivare
Department of Chemistry, J.J.T. University, Rajasthan, India

Synthesis of new series of N-substituted phenyl succinimide and glutarimide derivatives for the study of their antifungal activity

RS Dhivare, SS Rajput and R Yadav

Abstract
A new series of N-substituted phenyl cyclic imides were synthesized via reaction between succinic, glutaric anhydride and primary aromatic amines in presence of benzene and acetyl chloride. The synthesized derivatives were characterized by IR, ^{1}HNMR and ^{13}CNMR spectroscopy and antifungal activity behavior were studied using disc-diffusion method.

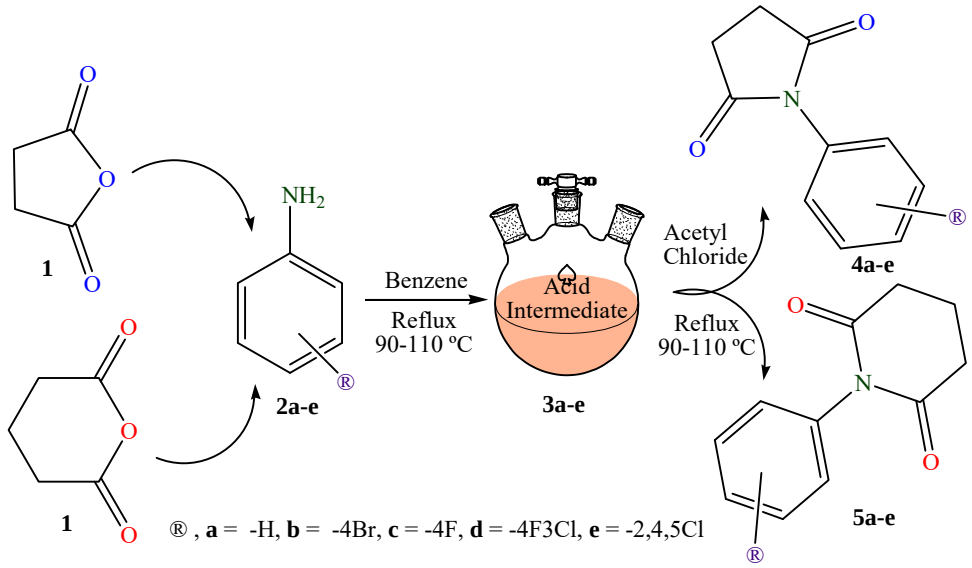
Keywords: N-Phenyl succinimides, N-Phenyl glutarimides, antifungal activity

Introduction
Cyclic imides containing the most common heterocyclic atoms like nitrogen, oxygen and sulphur play an important role in the development of pharmaceutical, chemical and agricultural fields. Succinimide performs the good electro-convulsions [1], nephrotoxic [2], anticonvulsant [3], anti-mutagenic [4], analgesic [5] activities. Some of the active succinimide derivatives found good antagonistic activity towards the guinea-pigs ileum [6]. Cyclic imides like succinimides, maleimides and itaconimide demonstrated the defensive and restorative antifungal influence against rice blast and kidney bean stem rots [7]. They also inhibit a selective mono-glyceride lipase and psychiatric disorders like anxiety and depression [8]. The number of succinimide derivatives showed the seedling growth stimulator activities against wheat and radish [9]. Some of the substituted six membered glutarimide derivatives are hydrophobic nature which reveals antibacterial and antifungal activities, Glutarimide drug also affect on the biological membranes [10]. Naturally isolated alkaloids like glutarimides from the species of croton pullei showed most excellent antifungal activities [11]. The synergistic effects of glutarimides actively found on spinal neurons [12], brain metabolism [13], mitochondrial respiration [14]. Therefore the synthesis phenyl substituted cyclic imides has been focus of active research area over the years [15, 16].

Materials and Methods
Melting points were noted by open glass capillaries and were uncorrected. IR spectra in KBr pallets) were recorded by using Shimadzu and ATR Brucker alpha FT-IR spectrophotometer. ^{1}HNMR and ^{13}CNMR spectra were recorded on 400 MHz and 500 MHz by Brucker spectrophotometer. TLC was monitored by using pre-coated silica gel aluminium plates with mixture of diethyl ether and ethyl acetate. All the compounds 4a-e and 5a-e were synthesized in hours from the corresponding commercial available aromatic amines, succinic anhydride, glutaric anhydride, and benzene, acetyl chloride.

General procedure for N-phenyl succinimides and glutarimides:
To succinic or glutaric anhydride (1mole) benzene was added and heated under reflux condensation with constant stirring for 15 to 20 minutes till the clear solution formed. Into this solution the mixture of substituted anilines (1mole) in 10 ml benzene was slowly pour out by continuous stirring up to 15 to 20 min till the solution becomes homogeneous. Upon evaporation of benzene the whitish acid intermediate powder of 3-*N*-phenyl propanoic acid or 4-*N*-phenylcarbamoyl butanoic acid was obtained. The further ring closing steps was performed by using acetyl chloride.
Then mixture of 3-*N*-phenyl propanoic acid and acetyl chloride (9mole) was reflux for 15 to 20 minutes till the complete evolution of HCl gas by the formation of *N*-phenyl succinimides.

By the same way the mixture of 4-(phenylcarbamoyl) butanoic acid and acetyl chloride (9mole) was reflux for 15 to 20 minutes till the complete evolution of HCl gas by the formation of *N*-phenyl glutarimides. (Scheme–I)



Scheme - I: Preparation of N-phenyl Succinimides and Glutarimides

1-phenylpyrrolidine-2, 5-dione (4a)
White solid, yield [79.91%], m. p. 154-156 ºC,M.F.$C_{10}H_9NO_2$,M.W. 175.06;IR (KBr): 1708, 1774, 2937, 1291, 1457, 1502, 1595 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.1-7.42 (m, 5H, Ar-H), 2.93 (s, 4H, imide)

1-(4-bromophenyl) pyrrolidine-2, 5-dione (4b)
Brownish solid, yield [89.78%], m. p. 174-176 ºC, M.F. $C_{10}H_8BrNO_2$,M.W. 254.08; IR (KBr): 1707,1766, 2998, 1295, 1455, 1488, 1588, 1070 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.16-7.40 (m, 4H, Ar-H), 2.95 (s, 4H, imide)

1-(4-fluorophenyl) pyrrolidine-2, 5-dione (4c)
Brownish solid, yield [62.90%], m. p. 176-178 ºC, M.F. $C_{10}H_8FNO_2$,M.W. 193.17; IR (KBr): 1712, 1767, 3000, 1290, 1456, 1513, 1604, 1178 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.16-7.36 (m, 4H, Ar-H), 2.94 (s, 4H, imide)

1-(3-chloro-4-fluorophenyl) pyrrolidine-2, 5-dione (4d)
Pinkish solid, yield [84.60%], m. p. 158-160 ºC, M.F.$C_{10}H_7ClFNO_2$,M.W. 227.62; IR (ATR): 1698, 1776, 2800, 1294, 1490, 1502, 1595, 1173, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 6.87-7.94 (m, 3H, Ar-H), 2.94 (s, 4H, imide)

1-(2, 4, 5-trichlorophenyl) pyrrolidine-2, 5-dione (4e)
Pure white solid, yield [75.56%], m. p. 196-198 ºC, $C_{10}H_6Cl_3NO_2$, M.W. 278.52; IR (ATR): 1660, 1700, 2993, 1356, 1454, 1508, 1570, 1072 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.39-7.53 (m, 2H, Ar-H), 2.95 (s, 4H, imide)

1-phenylpiperidine-2, 6-dione (5a)
Cream coloured solid, yield [77.92%], m. p. 120-122 ºC, M.F. $C_{11}H_{11}NO_2$, Mol. Wt. 189.21; IR (KBr): 1674, 1770, 2971, 1314, 1499, 1535, 1598 cm^{-1}

1-(4-bromophenyl) piperidine-2, 6-dione (5b)
Brownish solid, yield [82.94%], m. p. 144-146 ºC, M.F. $C_{11}H_{10}BrNO_2$, Mol. Wt. 268.11; IR (KBr): 1695, 1719, 2992, 1301, 1490, 1526, 1589, 1070 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.40-7.55 (d, 4H, Ar-H), 1.87 (m, 2H, $-CH_2-CH_2-CH_2-$), 2.226 (t, 4H, imide)

1-(4-fluorophenyl) piperidine-2, 6-dione (5c)
Brownish solid, yield [76.35%], m. p. 119-121 ºC, M.F. $C_{11}H_{10}FNO_2$, Mol. Wt. 207.2; IR (KBr): 1696, 1722, 2961, 1305, 1519, 1613, 1658, 1186 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.6-7.55 (d, 4H, Ar-H), 1.68 (m, 2H, $-CH_2-CH_2-CH_2-$), 2.15 (t, 4H, imide)

1-(3-chloro-4-fluorophenyl) piperidine-2, 6-dione (5d)
Brownish white solid, yield [91.30%], m. p. 104-106 ºC, M.F. $C_{11}H_9ClFNO_2$, Mol. Wt. 241.65; IR (ATR): 1638, 1700, 2951, 1312, 1497, 1546, 1600, 1191, 1055 cm^{-1}; ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 7.34-7.92 (m, 3H, Ar-H), 1.80 (m, 2H, $-CH_2-CH_2-CH_2-$), 2.28 (t, 4H, imide); ^{13}C NMR (125.77 MHz, DMSO-d_6, δ ppm): 20.72, 33.35, 35.75, 39.95, 117.19, 119.70, 120.82, 136.93, 152.35, 154.29, 171.42, 174.56

1-(2, 4, 5-trichlorophenyl) piperidine-2,6-dione (5e)
Pure white solid, yield [85.73%], m. p. 138-140 ºC, M.F. $C_{11}H_8Cl_3NO_2$, Mol. Wt. 292.55; IR (ATR): 1665, 1697, 2968, 1306, 1457, 1513, 1570, 1076 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$, δ ppm): 7.28-7.49 (d, 2H, Ar-H), 2.10 (m, 2H, $-CH_2-CH_2-CH_2-$), 2.27 (t, 4H, imide)

Results and Discussion

Chemistry

The series of substituted phenyl succinimides 4a-e and glutarimides 5a-e by ring opening reaction of acid intermediates given excellent yields by the action of acetyl chloride ring closing reaction. The final derivatives were confirmed by IR, ^{1}HNMR, ^{13}CNMR and elemental annals.

Antifungal activities

All the synthesized compounds 4a-e and 5a-e were send for their antifungal activity using DMSO solvent against *Candida albicans* NCIM 3471 and *Aspergillus niger* NCIM 545 strains as shown in the table 1. Amphotericin-B used as a standard drug for taking antifungal activities.

Table 1: Antifungal activities of N-phenyl succinimides and glutarimides

Compd Code	Zone diameter in mm against *Candida albicans* NCIM 3471 (Mean ± SD)	Zone diameter in mm against *Aspergillus niger* NCIM 545 (Mean ± SD)
	100 µg/ml	100 µg/ml
4a	9.63 ± 0.23**	12.62 ± 0.33**
4b	--	--
4c	13.19 ± 0.15*	16.41 ± 0.42**
4d	14.68 ± 0.18**	15.56 ± 0.37**
4e	7.41 ± 0.27**	--
5a	--	--
5b	--	--
5c	--	--
5d	--	--
5e	--	--
Std	12.40 ± 0.43	10.45 ± 0.11
Keynote: *Zone of inhibition measured in mm (-- means no zone)*		

Statistical Analysis

The complete results of the synthesized compound 4a-e and 5a-e series were calculated by triplicate methods N=3 with the mean plus standard deviation indicated in the graph-1. The statistical significance was accessed by one way ANOVA and Dunnett Multiple Comparisons Test performed by the standard drug against synthesized compounds. P value < 0.05 was considered as statistically significant remarked by *p<0.05, **p<0.01 compared to standard group.

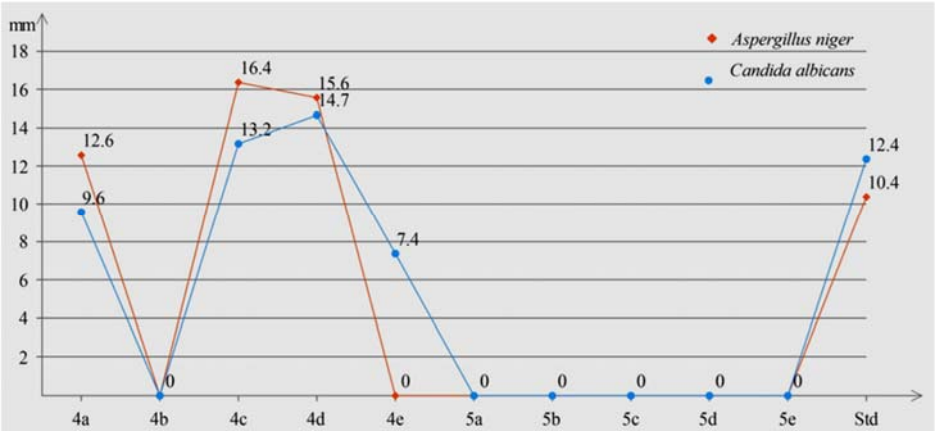


Fig 1: Antifungal activities of 4a-e and 5a-e

Conclusion

Heterocyclic derivatives of cyclic imides perform the fundamental title role with their biological entities. By antifungal point of view 4a and 4e compounds showed moderate antifungal activities against *Candida albicans* fungal species. The compound 4c and 4d are synergistically very potent against *Candida albicans* and *Aspergillus niger* fungal strains. Almost all the glutarimide series are inactive against both fungal strains. These compounds could make the most of innumerable heterocyclic synthesis.

References

1. Luszczki JJ, Marzeda E, Kondrat-Wrobe MW, Wrobel J, Kocharov SL, Florek-Luszczki M. Journal of Preclinical and Clinical Research. 2014; 8(1):34-37.
2. Hudkins RL, DeHaven-Hudkins DL, Doukas P. Bioorganic and Medicinal Chemistry Letters, 1997; 7(8):979-984.
3. Obniska J, Rzepka S, Krzysztof KS. Elsewhere, Bioorganic and Medicinal Chemistry. 2012; 20:4872-4880.
4. Pekalaa E, Lianaa P, Kubowicza P, Powroznika B, Obniska J, Chebekb I *et al*. Elsewhere, Mutation Research. 2013; 758:18-22.
5. Muszalska I, Acta Poloniae Pharmaceutica and Drug Research. 2010; 67(3):233-238.
6. Lindquist A, Ringdahl B, Svensson U, Dahlbom R, Acta Chemica Scandinavica, 1976; B(30):517-520.
7. Fujinami A, Ozaki T, Nodera K, Tanaka K. Agr. Biol. Chem. 1972; 36(2):318-323.
8. Matuszak N, Muccioli GG, Labar J, Lambert DM. Journal of Medicinal Chemistry. 2009; 52:7410-7420.
9. Allen SE, Skoog F. American Society of Plant Biologist. 1950, 179-183.
10. Michalska D, Morzyk B, Bienko DC, Wojciechowski W, Medical Hypotheses, 2000; 54(3):472-474.
11. Rosana NS Peixoto, Giselle MSP. Guilhon. *et al*., Molecules. 2013; 18:3195-3205.
12. Nicholson GM, Spence I, Johnston GAR. Elsevier, Neuropharmacology. 1985; 24(6):461-464.
13. Nicholls PJ. International Journal of Neuropharmacology, 1962; 1(1-3):229.
14. Prado SRT, Cechinel-Filho V, Campos-Buzzi F, Correa R, Cadena SMS, Martinelli de Oliveira M. B., Z. Naturforsch. 2004; 59c:663-672.
15. Patil MM, Rajput SS. International Journal of Pharmacy and Pharmaceutical Sciences. 2014; 6(11):8-14.
16. Rajput SS. International Journal of Advances in Pharmacy, Biology and Chemistry. 2012; 1(2):242-246.