International Journal of Sciences & Applied Research

www.ijsar.in

Synthesis and anticonvulsant activity of some semicarbazone derivatives of some carbonyl compounds

Ashok Kumar[1]*, S. B. Singh[2], Galal M. Zaiad[3], Ismail Awheda[4]

[1]Department of Chemistry, DDPGU, Murlipur, CSJMU, Kanpur, India.
[2]Pandit Om Prakash Sharma Degree College Rura CSJMU, Kanpur India.
[3]Department of Chemistry, Al-mergheb University, Faculty of Science, Al-khoms, Libya.
[4]Department of Chemistry, Al-mergheb University, Faculty of Science, Al-khoms, Libya.
Corresponding author: *Ashok Kumar, 109 M.I.G. Ratan Lal Nagar, Kanpur-208022, India.

Abstract
A search of new potent anticonvulsant drugs continues to be an active area of investigation in medicinal chemistry. Although several new anticonvulsant drugs are already in clinical use, some types of seizures are still not adequately treated with current therapy and have limitations, intolerable side effects. Keeping this in mind, the present work was carried out to synthesize a series of semicarbazones to get the compound with lesser side effects and more potent anticonvulsive agents. The present study describes the synthesis of newer semicarbazone derivatives by the condensation reaction of ketones and semicarbazides and their anticonvulsant activity was tested by using standard maximal electroshock (MES) induced seizures in mice and subcutaneous strychnine threshold test (ScSty) in rats using dose 100 mg/kg, intraperitoneally, and neurotoxicity screening was assessed by applying rotarod test in mice. Most of the compound exhibited potent anticonvulsant activity and more safer than the standard drug, phenetoin. Among all compounds, compounds SCZ3 & SCZ4 produced most potent anticonvulsant effect.

Keywords: Synthesis, Semicarbazones, Anticonvulsant activity, Neurotoxicity

1. INTRODUCTION

Epilepsy is a common neurological disorder. Different types of seizures may have different neurological basis and are to be controlled with different medications. In this regard, hydantoins, bezodiazepines and more recently remacemide have been used as antiepileptic drugs. For the last few years semicarbazones have investigated as novel anticonvulsants (Dimmock et al.1996 ; Pandeya et al. 1998; Dogan et al.1999). These compounds have been evaluated for their anticonvulsant properties using two screens namely the maximal electroshock (MES) and subcutaneous strychnine (ScSTY) induced seizure tests. These compounds have shown greater protection in the MES test than in the ScSTY screen. Further these compounds were inactive in the ScSTY screen after oral administration to rats.

Recently a theory has been promulgated, thereby, for MES activity, the aryl ring and semicarbazono group interact at two

locations on a receptor (Pandeya et al. 1999),. These two locations are called the aryl binding site and the hydrogen bonding area. The terminal $–CONH_2$ group of the semicarbazono group is implicated in the hydrogen bonding process. These new aspects encouraged us to synthesize new semicarbazone derivatives in search of potential anticonvulsant drugs.

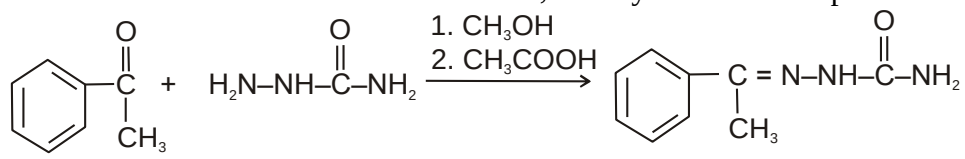
2. MATERIALS AND METHODS

The melting points of the compounds were determined in open capillary tubes on a Thomas Hooker melting point apparatus (Perfit) and are uncorrected. IR spectra were recorded in KBr pellets and JASCO FTIR-5300 infrared spectrophotometer (Japan) ^{1}H-NMR spectra were determined at 300.40 MH_2 JEOL-AL 300 (Fourier Transform, Japan) (300.40 MHz) JEOL FX 90Q (90 MHz) (Japan) and Mercury Plus Varian (400 MHz) spectrometers with tetramethylsilane as internal standard.

2.1. Synthesis of semicarbazones **:** Various semicabazone derivatives were synthesized by the condensation reaction of appropriate molar concentration of semicarbazide with corresponding cyclic/ aryl ketones mentioned as below –

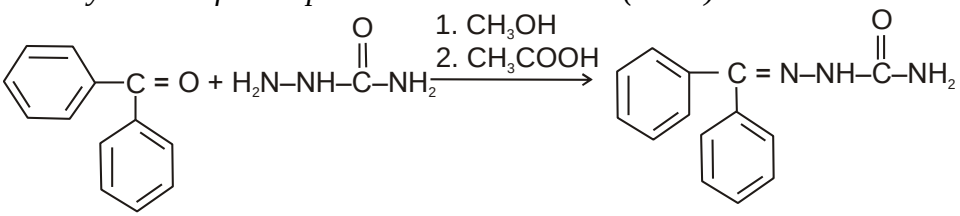
2.1.1.*Synthesis of acetophenone semicarbazone (SCZl)*

Acetophenone (10 ml, 0.056 mol) was taken in a round bottom flask and 10 ml semicarbazide was added and make alkaline solution by adding 10 ml methanol solution with 10 ml glacial acetic acid and heated in a distillation unit, then synthesized compound was dried and collected.



Acetophenone Semicarbazide (SCz1)

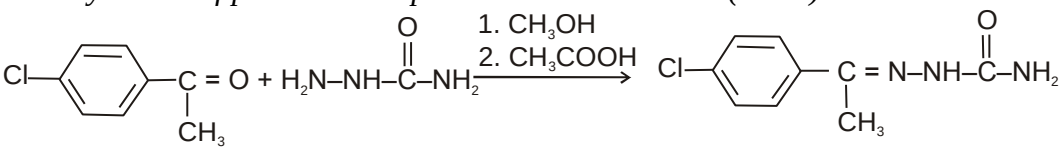
2.1.2.*Synthesis of benzophenone semicarbazone (SCZ2)*



(SCz2)

The (0.041 mol) of benzophenone and 10 ml hydrazine hydrate in a round bottom flask of 500 ml and make alkali the solution by adding 10 ml methanol and then neutralized by adding 10 ml glacial acetic acid and heated in a distillation unit upto 1.5-2.5 h and synthesized compound was dried and collected.

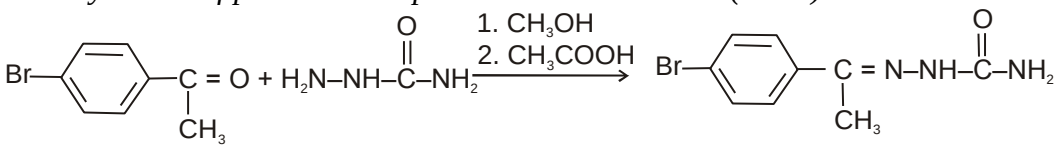
2.1.3.*Synthesis of p-chloroacetophenone semicarbazone (SCZ3)*



(SCz3)

The 10 ml (0.047 mol) p-chloroacetophenone solution and 10 ml of hydrazine hydrate were taken in a RBF of 500 ml and make solution alkali by adding 10 ml of methanol and the neutralizing of glacial acetic acid and heating in a distillation unit. Synthesized compound were dried and collected.

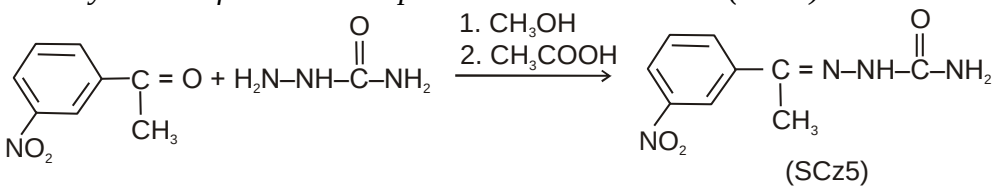
2.1.4.*Synthesis of p-bromoacetophenone semicarbazone (SCZ4)*



(SCz4)

The 10 ml (0.039 mol) of p-bromoacetophenone solution and 10 ml of hydrazine hydrate solution was taken in a RBF (500 ml) and 10 ml methanol was then added 40 ml glacial acetic acid and heating in a distillation unit. Synthesized compound were dried and collected.

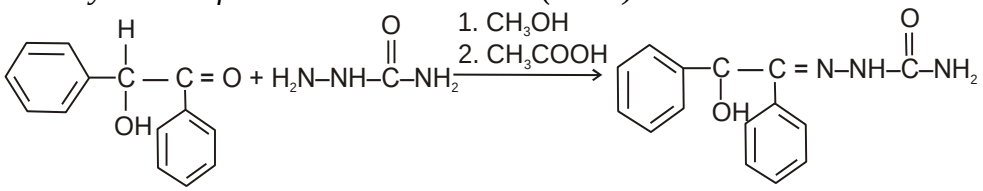
2.1.5.*Synthesis of m-nitroacetophenone semicarbazones (SCZ5)*



(SCz5)

The 10 ml (0.45 mol) of m-nitroacetophenone solution and have been taken in a RBF (500 ml) and add 10 ml methanol then 10 ml glacial acetic acid and heating in distillation unit. Synthesized compound were dried and collected.

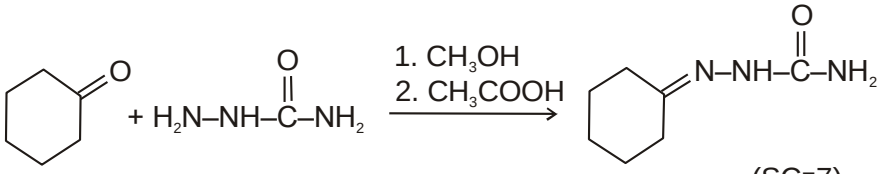
2.1.6.*Synthesis of benzoin semicarbazone (SCZ6)*



(SCz6)

The 10 ml (0.037 ml) of benzoin and 10 ml hydrazine hydrate solution was taken in a RBF (500 ml) and 10 ml methanol and 10 ml glacial acetic acid were added in it. The mixture distillation in a distillation unit and synthesized compound were dried and collected.

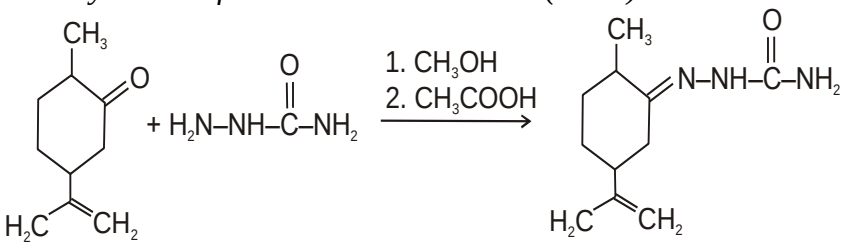
2.1.7.*Synthesis of cyclohexone semicarbazone (SCZ 7)*



(SCz7)

1 gm cyclohexane and 10 ml (0.73 mol) of hydrazine hydrate solution was taken in a RBF (500 ml) and 10 ml methanol and 10 ml of glacial acetic acid was added and mixture was distillated in distillation unit and synthesized compound dried and collected.

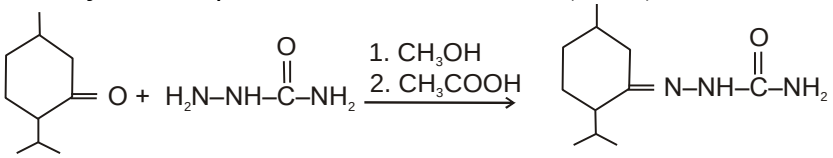
2.1.8.*Synthesis of carvone semicarbazone (SCZ8)*



(SCz8)

1 gm carvone and 10 ml (0.049 mol) of hydrazine hydrate were taken in a RBF (500 ml) and 10 ml methanol and 10 ml of glacial acetic acid were added and mixture was heated in a distillation unit and synthesized compound dried and collected.

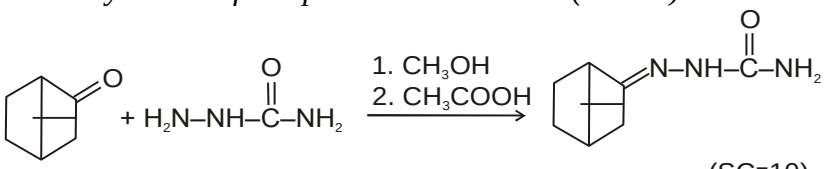
2.1.9.*Synthesis of menthone semicarbazone (SCZ9)*



(SCz9)

1 gm methone (0.047 mol) and 10 ml of hydrazine hydrate were taken in a RBF (500 ml) and 10 ml methanol and 10 ml of glacial acetic acid was added mixture was heated in a distillation unit and synthesized compound dried and collected. Yield = 88%

2.1.10.*Synthesis of camphor semicarbazone (SCZ10)*



(SCz10)

1 gm camphor (0.047 mol) and 10 ml of hydrazine hydrate were taken in a RBF (500 ml) and 10 ml methanol and 10 ml of glacial acetic acid was added. The mixture was heated in a distillation unit and the synthesized compound dried and collected.

2.2.Screening of Anticonvulsant activity

Initially all the compounds were administered i.p. in a concentration volume of 0.01 mL/body weight for mice and 0.004 mL/g body weight for rats at doses of 30, 100 and 300 mg/kg to one of the four animals. The profile of anticonvulsant activity was established after i.p. injections by one electrical and two chemical tests. The electrical test employed was the maximal electroshock seizure (MES) test and the chemical test employed was the subcutaneous strychnine (ScSTY) seizure threshold test.

2.2.1.*Maximal electroshock-induced seizures test (MES)*

Anticonvulsant activity of the compounds was tested using reported procedure (Krall et al., 1978).Maximal electroshock seizures were elicited with a 60-cycle alternating current of 50 mA intensity delivered for 0.2 seconds via corneal electrodes. A drop of 0.9% saline was instilled in eyes prior to application of the electrodes in order to prevent the death of the animal. The mice were previously administered i.p. with the test compound solution. Abolition of the hind limb tonic extensor spasm was

recorded as a measurement of protection against seizures i.e. anticonvulsant activity.

2.2.2.*ScSTY-induced seizure threshold test*

This test was perfomed for the measurement of anticonvulsant action using method of Lapin, 1981. The ability of the test compounds to provide a protection against seizures was measured 30 min. after administration. Albino rats were used as experimental animals. Protection or anticonvulsant action was defined as the abolition of the hind leg extensor component of the seizure induced by 2 mg/kg, s.c. injection of strychinine.

2.2.3. *Neutrotoxicity (NT) Screen*

Minimal motor impairment was measured in mice by the rotorod test (Kinnard, 1957). The mice were trained to stay on an accelerating rotorod that rotates at two revolutions per minute. The rod diameter was 3.2 cm. Trained animals were given i.p. injection of the test compounds. Neutrotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of three trials.

3. RESULTS AND DISCUSSION

Physical, chemical and spectral data of all the synthesized compounds are given in Table 1&2. Structure of all the compounds were confirmed by elemental analysis, IR and NMR spectra.

Anticonvulsant activity screen and neurotoxicity (NT) data are given in Table 3. Anticonvulsant activity test data of all compounds and phenetoin, the reference prototype anti epileptic drug, were recorded under the same conditions. Compounds SCZ1, SCZ2, SCZ3, SCZ4, SCZ5, SCZ6, SCZ7 , SCZ9 after 0.5h of compounds administration and compounds SCZ3, SCZ4 after 4h of compounds administration were found to have most potent anticonvulsant action at the dose of 100 mg/kg,i.p. in mice, and test compounds SCZ4 and SCZ9 shows most potent anticonvulsant activity after 24 h of test compounds administration at the dose of 100 mg/kg,i.p. in mice. In ScSTY screen, most of the compounds possessed anticonvulsant activity after 0.5h and 4h of test compounds administration in dose of 100 mg/kg,i.p.in rats, however, compound SCZ3 was found most potent after 0.5 h of test compound administration in dose of 100 mg/kg,i.p. in rats. It was observed from the results of Rota-rod test that all the test compounds did not show neurotoxicity at dose of 100 mg/kg,i.p in mice, however, neurotoxicity was found in all the compounds at the dose of 300 mg/kg, i.p. of test compounds administration.

It is apparent from the above anticonvulsant activity tests data that compounds SCZ3 and SCZ4 have shown most potent action in shorter duration of time (0.5h after administration) at dose of 100 mg/kg, i.p.in animals with no sign of neurotoxicity. It also seems that presence of halogen substituent of para position of aryl ring of acetophenone increases the potency of semicarbazone derivatives. Activity of these compounds might be due to the presence of hydrogen bonding domain and aryl ring with high electronegative substituent at para position which is lipophilic (Yogeshwai et al. 2000; Siddiqui et al. 2007).

Table-1: Physical and Chemical data of semicarbazones

Comp. Code	Molecular formula	Molecular weight	M. P. ^{o}C	C.H.N.					
				Calculated			Observed		
SCZ1	$C_9H_{11}N_3O$	177	199	61.01	6.21	23.72	61.09	6.29	23.68
SCZ2	$C_{14}H_{13}N_3O$	239	186	70.29	5.43	17.57	70.49	5.64	17.77
SCZ3	$C_9H_{10}N_3ClO$	211.5	201	51.06	4.72	19.85	51.12	4.94	19.98
SCZ4	$C_9H_{10}N_3OBr$	256	208	42.18	3.90	16.40	42.30	3.99	16.60
SCZ5	$C_9H_{10}N_4O_3$	222	257	48.64	4.50	25.22	68.92	4.85	25.46
SCZ6	$C_{15}H_{15}N_3O_2$	269	206	66.91	5.57	15.61	66.99	5.69	15.91
SCZ7	$C_7H_{13}N_3O$	155	167	54.19	8.38	27.09	54.21	8.39	27.02
SCZ8	$C_{11}H_{14}N_3O$	204	163	64.70	6.86	20.58	64.90	6.95	20.85
SCZ9	$C_{11}H_{21}N_3O$	211	189	62.55	9.95	19.90	62.75	9.99	19.98
SCZ10	$C_{11}H_{19}N_3O$	209	238	63.15	9.09	20.09	63.32	9.30	20.26

Table-2: Spectral data of the semicarbazone derivatives

S. No.	Compound Name	Compd Code	IR KBr V cm^{-1}	^{1}HNMR (d_6-DMSO) δ ppm
1.	Acetophenone semicarbazone	SCZ1	3470 (NH), 2998 (CH) 1610 (C=N) 1725 (CO)	6.1 (S, 2H, NH_2), 0.9 (S, 3H, CH_3), 7.0 (S, 1H, NH)
2.	Benzophenone semicarbazone	SCZ2	3480 (NH), 3010(CH) 1725 (CO) 1640 (C=N)	6.0 (S, 2H, NH_2), 6.8 (S, 1H, NH), 7.4-7.7 (m, 10H, Ar-H)
3.	p-Chloroacetophenone semicarbazone	SCZ3	3472 (NH) 3020 (CH) 1630 (C=N) 1728 (CO)	6.3 (S, 2H, NH_2), 0.9 (S, 3H, CH_3) 7.1(S, 1H, NH), 4.3 (S, 8H, CH_3)
4.	p-Bromoacetophenone semicarbazone	SCZ4	3470 (NH) 3010 (CH) 1624 (C=N) 1740 (CO)	6.2 (S, 2H, NH_2), 0.8 (S, 3H, CH_3) 7.0(S, 1H, NH), 4.0 (S, 8H, CH_2)
5.	M-nitroacetophenone semicarbazone	SCZ5	3458 (NH) 2990 (CH) 1626 (C=N) 1732 (CO)	6.0 (S, 2H, NH_2), 0.9 (S, 3H, CH_3) 7.1(S, 14H, NH), 6.9(S, 2H, CH_3), 5.8 (S, 4H, CH_2)
6.	Benoin semicarbazone	SCZ6	3460 (NH) 3300 (OH) 2992 (CH) 1728 (CO) 1628 (C=N)	4.0 (S, 1H, OH), 6.1 (S, 2H, NH_2) 7.0(S,1H,NH) 7.3-7.8 (m,10H,Ar-H)
7.	Cyclohexanone semicarbazone	SCZ7	3475 (NH) 2980 (CH) 1730 (CO) 1630 (C=N)	1.3 (m, 10H, $5CH_2$), 5.8 (S, 2H, NH_2) 6.9 (S, 2H, NH)
8.	Carvone semicarbazone	SCZ8	3476 (NH) 2996 (CH) 1748 (CO) 1710 (C=N)	5.9 (S, 2H, NH_2), 0.9 (S, 6H, $2CH_3$), 0.9 (S, 6H, $2CH_3$) 7.0(S, 1H, NH) 2.9 (m, 6H, $3CH_2$)
9.	Menthone semicarbazone	SCZ9	3470 (NH) 3020 (CH) 1620 (CO) 1726 (C=N)	5.8 (S, 2H, NH_2), 0.8 (S, 9H, $3CH_3$) 7.0(S, 1H, NH), 3.0(m, 6H, $3CH_3$)
10.	Camphour semicarbazone	SCZ10	3480 (NH) 3033 (CH) 1645 (CO) 1720 (C=N)	6.2 (S, 2H, NH_2), 0.9 (S, 6H, $2CH_3$) 6.9(S, 1H, NH), 2.8 (m, 6H, $3CH_3$)

Table 3: Anticonvulsant activity of semicarbazones

Compd. code	Doses mg/kg	MES screen			ScSTY screen			Neutrotoxicity doses*
		0.5h	4h	24h	0.5h	4h	24h	mg/kg
SCZ1	100	1/3	0/3	0/3	1/3	1/3	Death	300
SCZ2	100	1/3	1/3	2/3	0/3	0/3	Death	300
SCZ3	100	3/3	2/3	2/3	3/3	2/3	1/3	300
SCZ4	100	3/3	1/3	3/3	2/3	2/3	1/3	300
SCZ5	100	1/3	1/3	2/3	1/3	1/3	2/3	300
SCZ6	100	1/3	2/3	0/3	0/3	1/3	1/3	300
SCZ7	100	2/3	0/3	1/3	1/3	0/3	Death	300
SCZ8	100	0/3	2/3	0/3	1/3	0/3	Death	300
SCZ9	100	1/3	2/3	3/3	1/3	2/3	2/3	300
SCZ10	100	0/3	0/3	0/3	1/3	1/3	1/3	300
Phenytoin	30	3/3	3/3	2/3	-	-	-	100

*All compounds did not show neurotoxicity at dose of 100 mg/kg, i.p. after 0.5h & 4h of compounds administration but it was found at dose of 300mg/kg,i.p.

CONCLUSION

Anticonvulsant activity of the synthesized compound was performed successfully. Most of the compounds have demonstrated significant anticonvulsant effect, Compounds SCZ3 and compound SCZ4 were found to have most potent anticonvulsant action after 0.5 h of 100 mg/kg,i.p. dose of their administration in animals. These compounds did not produce any sign of neurotoxicity. Our results as discussed above support in future design and development of novel semicarbazones for the treatment of epilepsy.

REFERENCES

1. Dimmock, J.R., Puthucode, R.N., Lo, M.S., Quail, J.W.,Yang, J., Stables, J.P., 1996. Structural modifications of the primary amino group of anticonvulsant aryl semicarbazones. Pharmazie, 51, 83-8
2. Pandeya, S.N., Mishra, V, Singh, P.N., Rupainwar, D.C.,1998.Anticonvulsant activity of thiouriedo derivatives of acetophenone semicarbazone. Pharmacol. Res. 37, 17-22.
3. Pandeya, S.N, Aggarwal, N., Jain, J. S.,1999.Evaluation of semicarbazones for anticonvulsant and sedative hypnotic properties. Pharmazie, 54, 300 -02.
4. Dogan, H.N., Duran, A., Yemni, E.1999. Drug Metab. Drug Interact, 15, 187.
5. Krall, R.L., Penry, J.K., White, B.G., Kupferberg, H.J.,Swinyard, E.A.1978 Antiepileptic drug development: II. Anticonvulsant drug screening. Epilepsia, 19,409-498.
6. Lapin, I.P.1981 , Kinurenines and seizures. Epilepsia, 22, (3).
7. Kinnard ,W.J. Jr, Carr, C.J.1957. J Pharmacol Exp Ther , 121, 354-61.
8. Yogeshwari, P., Sriram, D., Thirumurgan, R., Rakhra, K.Sarasvat, V. 2000, Synthesis of N^4 –(2,4-dimethylphenyl) semicarbazones as 4-aminobytyrate aminotransferase inhibitors. Acta Pharm.,56, 259-72.
9. Siddiqui, N.,Khan, S.A.,Stables,J., Rana, A., Alam, M., Arshad, M.F.,Bhat, M.A. 2007. Synthesis and anticonvulsant activity of sulphonamide derivatives-hydrophobic domain. Bioorg. Med. Chem. Lett. 2007, 17,235-59.