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Synthesis and Utilization of Saccharin Derivatives

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ABSTRACT

Saccharin derivatives could be readily prepared from inexpensive and readily available materials and used these derivatives for the organic transformations. These compounds were well characterized by spectral data (NMR, MS).

Graphical Abstract

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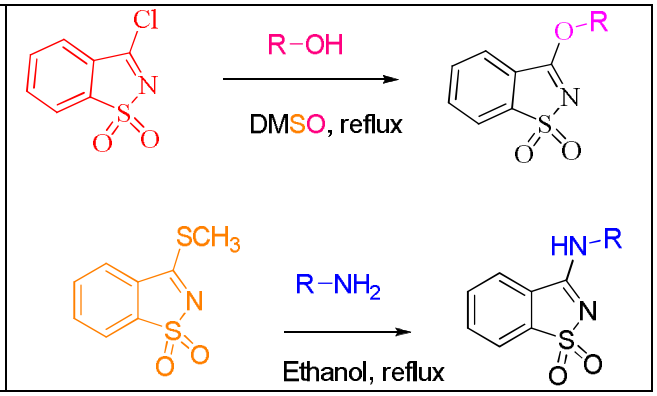


Keywords: Saccharin, ethers, amines, aldehydes, alcohols.

INTRODUCTION

Saccharin,1,2-benzisothiazole-3-one-1,1-dioxide, is a well known heterocyclic compound and has been used as a sweetener in the form of its sodium salt since 1885. Yet it is also a heterocyclic molecule of pharmaceutical importance and one of the key structural element of certain CNS-active drugs[1]. Saccharin compounds have been intensively investigated due to its suspected cancerogenic nature[2]. Many biological activities have been attributed

to this group, which are known as inhibitors of serine proteases[3], cathepsin Gandproteinase 3[4], α1a and α1c adrenergic receptor antagonists[5], human mastcelltryptase inhibitors[6], analgesics[7], 5-HT1a receptors[8], aldehyde dehydrogenase inhibitors[9], anti-anxiety and antibacterial[10]. Additionally, saccharinate complexes with amine derivatives have been useful as antidote for metal poisoning[11] and DNA-alerting ability[12]. Its importance has increased over the years and it can be viewed as a privileged scaffold in the field of medicinal chemistry. This particular heterocycle can either be a substituent of a larger compound that assumes the role of a frame work, or it can play the role of the pharmacophore of bioactive molecules[13]. It was also employed in the synthesis of phenolic ether prodrugs, with the intention of increasing their oral bioavailability[14]. Being a weak acid, saccharin readily forms salts with various basic active pharmaceutical ingredients (API) thus resulting in highly soluble saccharinates, which may be used above all in pediatric medication, on account of saccharin being a potent sweetenerable to mask the bitter taste of many drugs[15]. The use of saccharin acting as a co crystal former was also reported. Behaving both like a hydrogen bond donor and acceptor, it forms highly soluble co crystals with certain APIs[16].

It is a cheap and versatile starting material for the synthesis of related heterocyclic derivatives. Among those derivatives, 3-substituted ones are readily accessible through direct nucleophilic additions to the carbonyl carbon using strong nucleophiles such as alkyl and aryllithium reagents or corresponding Grignard reagents[17]. The substitution reactions proceed at monoaddition or diaddition stage depending on the reagents and reaction conditions. The monoaddition reactions lead to 3-substituted saccharins, while the diadditions provide benzosultam analogue[18]. Saccharin ether derivatives were reported by using palladium[19]. Heterocycles incorporating a sulfamido moiety have been reported to possess a variety of interesting biological activities. We are now reporting the series of saccharin ether derivatives synthesized and all the compounds were well characterized by spectral and analytical data.

MATERIALS AND METHODS

General: Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$or DMSO-$d_6$solution by using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. MS spectra were obtained on a mass spectrometer. All chemicals and reagents were purchased from commercial sources and purified before use.

General procedure for the Synthesis of saccharin ether derivatives (3a-i): A solution of thiomethyl saccharin(1 mmol) and alcohol(1.2 mmol) in 50ml DMSO then mixture was reflux for 1-5 h. After completion of the reaction (monitored by TLC) the mixture was cooled to room temperature .Pour over crushed ice and solid separated out was filtered. The organic product was extracted with diethyl ether (3×30ml) and the ethereal solution dried over anhydrous sodium sulphate, filtered, and the filtrate evaporated to dryness to give a colorless solid which was recrystallized from ethanol.

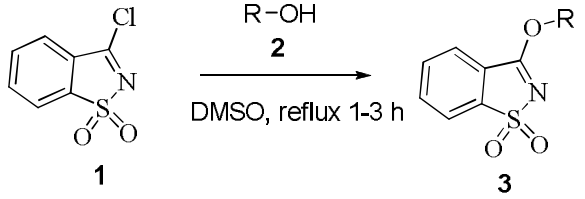
General procedure for the Synthesis of amino saccharin derivatives (6a-c): A solution of thiomethyl saccharin(1 mmol)and amine(1.2 mmol)in 50ml ethanol then mixture was reflux for 4-5 h. After completion of the reaction (monitored by TLC) the mixture was cooled to room temperature .Pour over crushed ice and solid separated out was filtered. Filtrate was extracted with dichloromethane work up and crystallized from hexane to afford the desired product.

General procedure for the Synthesis of iodo derivatives (7a-c and 8a-c): Corresponding KF/KBr/KI was dissolved in dry DMF followed by saccharin ether and 2ml of BF_3Et_2O was added and then refluxed for 1 h. After completion of the reaction (monitored by TLC) the mixture was cooled to room temperature. Pour over crushed ice and solid separated out was filtered to afford the desired product.

RESULTS AND DISCUSSION

The key starting materials chlorosaccharin (1) and thiomethyl saccharin (2) were prepared from cheaply available saccharin by reported procedures[20,21]. Chloro saccharin (**1**) was reacted with variety of alcohols (**2)** in DMSO at reflux and results are presented in Table 1. The reaction proceeded well in all these cases and the substituents like

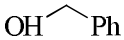
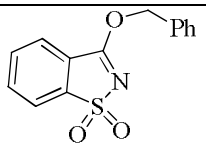
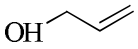
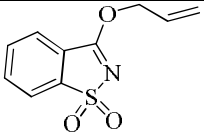
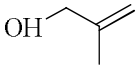
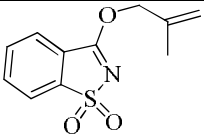
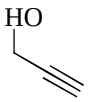
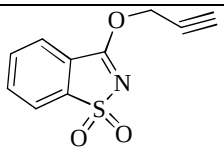
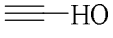
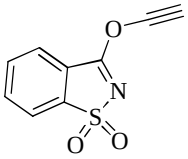
aromatic and aliphatic present in the alcohols (**2**) were well tolerated. The reaction appeared to be clean as no formation of side product was observed and the desired product **3** was isolated in good to excellent yield in each case. All the compounds synthesized were well characterized by spectral (NMR, MS).

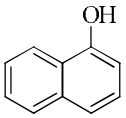
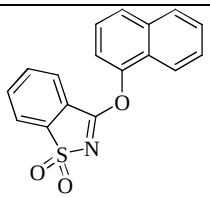
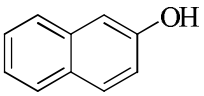
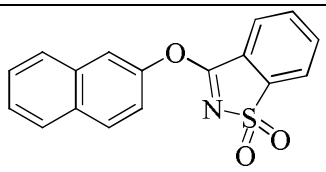
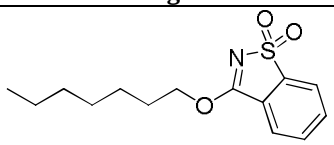
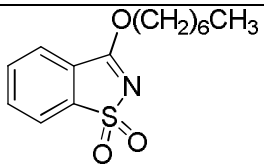
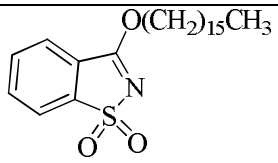


Scheme1. Synthesis of saccharin ether derivatives (**3a-i**)

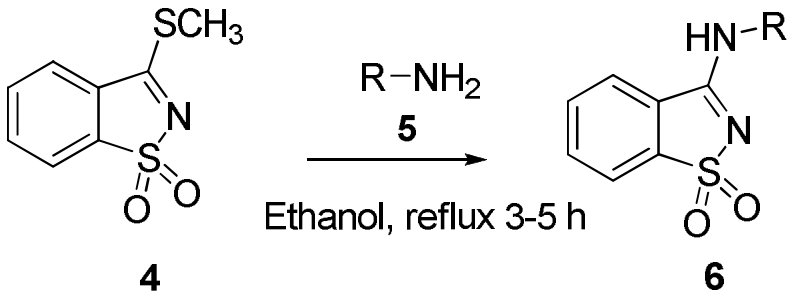
Thiomethylsaccharin (**4**) was reacted with variety of amines (**5**)in ethanol at reflux and results are presented in Table 2. The reaction proceeded well in all these cases and the substituents like cyclic and aliphatic present in the amines (**5**) were well tolerated. The reaction appeared to be clean as no formation of side product was observed and the desired product **6** was isolated in good to excellent yield in each case. All the compounds synthesized were well characterized by spectral (NMR, MS) data.

Table 1. Synthesis of saccharin ether derivatives (**3a-i**) from **1** (Scheme 1).[a]

Entry	(**2**)	Product (**3**)	Time (hours)	Yield[b] (%)
1		 **3a**	1	80
2		 **3b**	2	83
3		 **3c**	3	88
4		 **3d**	3	86
5			4	85

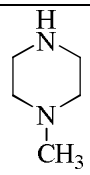
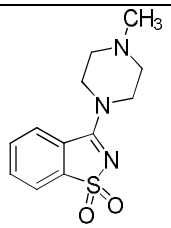
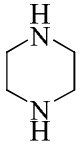
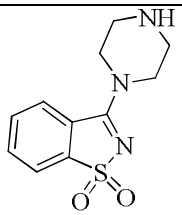
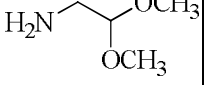
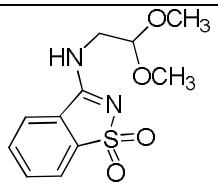
		3e		
6		 **3f**	2	86
7		 **3g**	2	88
8	CH_3-$(CH_2)_5$-CH_2-OH	 **3h**	5	82
9	$OH(CH_2)_6CH_3$	 **3i**	5	84
10	$OH(CH_2)_{15}CH_3$	 **3j**	5	85

[a]Reaction conditions: all the reactions were carried out using **1**(1.0 mmol), an appropriatealchol**2** (1.2mmol) and DMSO at reflux.[b]Isolated yield.



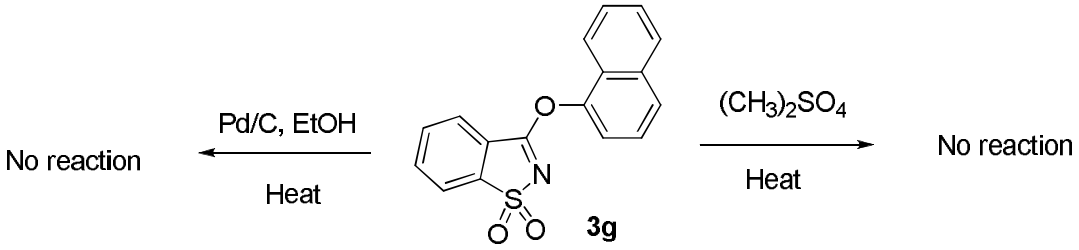
Scheme 2. Synthesis of amino substituted saccharin derivatives (**6a-d**)

Table 2. Synthesis of 3-amino substituted saccharin derivatives (**6a-d**) from 4 (Scheme 2).[a]

Entry	(**5**)	Product (**6**)	Time (hours)	Yield[b] (%)
1	 **5a**	 **6a**	3	85
2	 **5b**	 **6b**	4	88
3		 **6c**	4	80

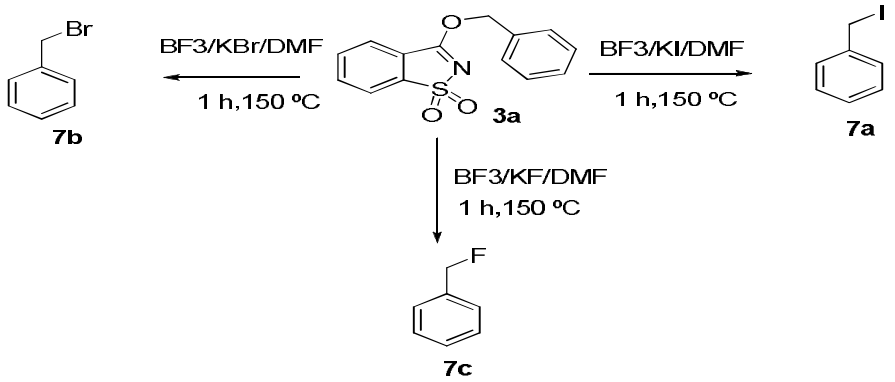
[a]Reaction conditions: all the reactions were carried out using **4**(1.0 mmol), an appropriate amine **5**(1.2 mmol) and Ethanol at reflux.[b]Isolated yield.

Structure elaboration of saccharin ether derivative (**3g**) we attempted methylation with dimethyl sulphate and reduction with pd/C but desired product was not obtained. There is no progress in reaction.

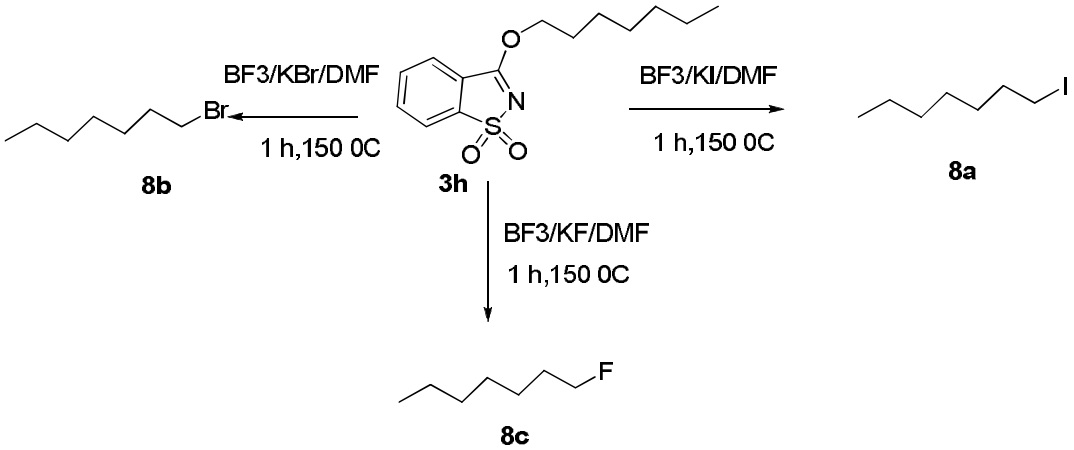


Scheme 3. Reactions attempted on saccharin ether derivative (**3g**)

Structure elaboration of saccharin ether derivative (**3a, 3h**) we attempted iodination, bromination and fluorination reactions. We observed corresponding halogenated products
7a-c and **8a-c**) were obtained.

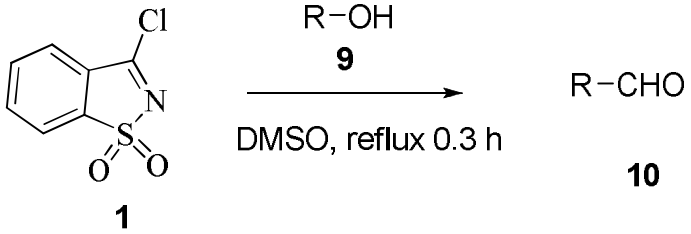


Scheme4. Synthesis of halo derivatives(**7a-c**)from saccharin ether derivative (**3a**)



Scheme5. Synthesis of halo derivatives(**8a-c**)from saccharin ether derivative (**3h**)

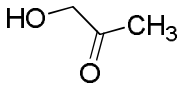
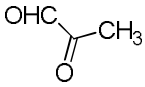
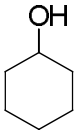
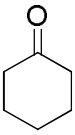
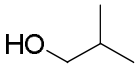
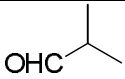
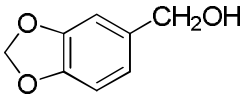
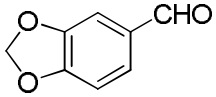
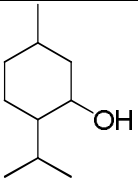
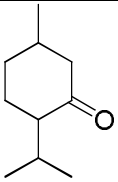
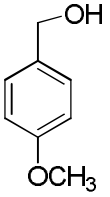
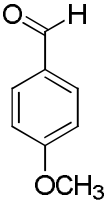
Chloro saccharin (**1**) was reacted with variety of alcohols (**9**)in DMSO at reflux and results are presented in Table 3. The reaction proceeded well in all these cases and the substituents like aromatic, cyclic and aliphatic present in the alcohols (**9**) were well tolerated. The reaction appeared to be clean as no formation of side product was observed and the desired product **10** was isolated in good to excellent yield in each case.



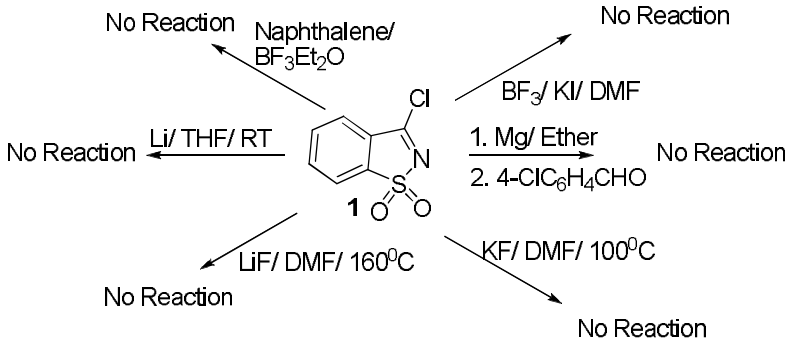
Scheme6. Synthesis of aldehyde derivatives(**10a-g**)from chloro saccharin (**1**)

Table 3. Synthesis of aldehyde derivatives(**10a-g**)from **1** (Scheme 6).[a]

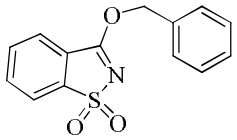
Entry	(**9**)	Product (**10**)	Time (hours)	Yield[b] (%)
1	CH_3-$(CH_2)_6$-OH	CH_3-$(CH_2)_5$-CHO **10a**	0.3	85

2		 **10b**	12	88
3		 **10c**	12	80
4		 **10d**	12	85
5		 **10e**	4	88
6		 **10f**	4	86
7		 **10g**	5	90

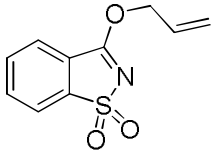
[a]Reaction conditions: all the reactions were carried out using **1**(1.0 mmol), an appropriate alcohol **9**(1.2 mmol) and DMSO at reflux.
[b]Isolated yield.



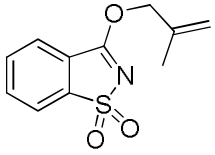
Scheme 7. Reactions attempted on chloro saccharin (**1**)



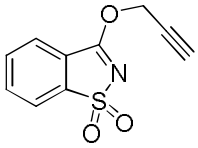
3a: White solid; mp: 130-132 ºC;[1]H NMR (400 MHz, DMSO-d_6) δ8.01-7.94 (m, 2H), 7.68-7.58 (m, 2H), 7.21 (s, 5H), 4.81 (s, 2H);[13]C NMR (100 MHz, DMSO-d_6) δ166.7, 141.3, 140.2, 134.5, 133.8, 132.6, 130.8, 129.5, 129.0, 127.4, 127.9, 65.7; EI-MS: m/z 274.04 $(M+H)^+$.



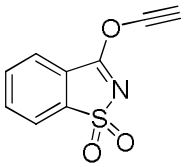
3b: White solid; mp: 124-126 ºC;[1]H NMR (400 MHz, DMSO-d_6) δ7.99-7.92 (m, 2H), 7.68-7.57 (m, 2H), 5.93-5.87 (m, 1H), 5.26-5.22 (m, 2H), 4.22 (s, 2H); [13]C NMR (100 MHz, DMSO-d_6) δ165.1, 140, 134.2, 133.5, 132.4, 130.7, 129.5, 128.6, 116.8, 64.5; EI-MS: m/z 224.2 $(M+H)^+$.



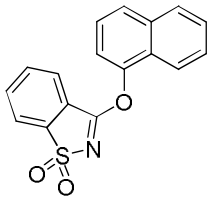
3c: White solid; [1]H NMR (400 MHz, DMSO-d_6) δ7.97-7.91 (m, 2H), 7.67-7.58 (m, 2H), 5.02 (d, J = 2.8 Hz, 1H), 4.98 (d, J = 2.8 Hz, 1H), 4.21 (s, 2H), 1.72 (s, 3H); [13]C NMR (100 MHz, DMSO-d_6) δ164.8, 140.8, 140.1, 134.2, 133.4, 132.3, 130.6,129.5, 128.5, 111.6, 67.8, 19.8;EI-MS: m/z 238.1 $(M+H)^+$.



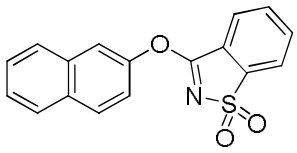
3d : White solid; [1]H NMR (400 MHz, DMSO-d_6) δ7.98-7.92 (m, 2H), 7.67-7.59 (m, 2H), 4.31 (s, 2H), 2.52 (s, 1H); [13]C NMR (100 MHz, DMSO-d_6) δ164.5, 140.5, 134.2, 132.8, 130.6, 129.7, 128.6, 79.2, 76.6, 52.9;EI-MS: m/z 222.01 $(M+H)^+$.



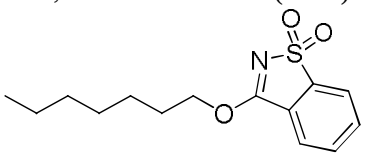
3e : White solid; [1]H NMR (400 MHz, DMSO-d_6) δ7.99-7.93 (m, 2H), 7.67-7.57 (m, 2H), 1.2 (s, 1H);[13]C NMR (100 MHz, DMSO-d_6) δ164.7, 140.3, 134.1, 132.5, 130.5, 129.6, 128.6, 75.3, 46.7; EI-MS: m/z 208.02 $(M+H)^+$.



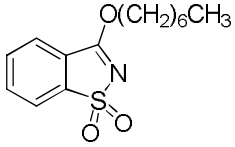
3f : White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ8.09 (d, J = 7.6 Hz, 1H), 8.01-7.94 (m, 2H), 7.62- 7.54 (m, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.39-7.31 (m, 3H), 7.20-7.16 (m, 1H), 6.64 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ165.7, 153.1, 140.2, 135.2, 134.9, 134.3, 132.5, 130.6, 129.5, 128.7, 128.2, 127.1, 126.9, 126.4, 121.9, 121.2, 109.6; EI-MS: m/z 310.04(M+H)$^+$.



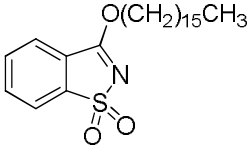
3g : White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ8.02-7.95 (m, 2H), 7.62- 7.54 (m, 5H), 7.31-7.21 (m, 2H), 7.01-6.98 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ165.6, 153.6, 140.2, 135.2, 134.3, 132.5, 130.7, 130.2, 129.5, 129.2, 128.7, 129.1, 126.9, 126.5, 124.1, 117.7, 109.8;EI-MS: m/z 310.04 (M+H)$^+$.



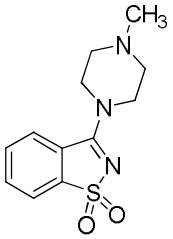
3h : Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ7.99-7.93 (m, 2H), 7.67-7.55 (m, 2H), 3.55 (t, J = 7.6 Hz, 2H), 1.49-1.46 (m, 2H), 1.29-1.34 (m, 8H), 0.99-0.96 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 140.1, 134.2, 132.3, 130.5, 129.5, 128.7, 62.5, 32.3, 30.6, 29.7, 25.9, 23.1, 14.3;EI-MS: m/z 282.1 (M+H)$^+$.



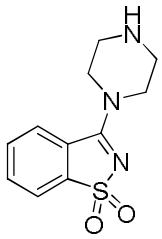
3i: Yellow solid; mp: 55-57 ºC;^{1}H NMR (400 MHz, DMSO-d_6) δ7.99-7.93 (m, 2H), 7.67-7.55 (m, 2H), 3.55 (t, J = 7.6 Hz, 2H), 1.49-1.46 (m, 2H), 1.29-1.34 (m, 8H), 0.99-0.96 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ165.2, 140.1, 134.2, 132.3, 130.5, 129.5, 128.7, 62.5, 32.3, 30.6, 29.7, 25.9, 23.1, 14.3.EI-MS: m/z 282.1 (M+H)$^+$.



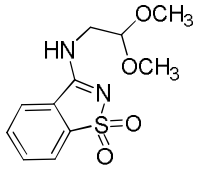
3j : Yellow solid; mp: 65-67 ºC;^{1}H NMR (400 MHz, DMSO-d_6) δ7.99-7.93 (m, 2H), 7.67-7.55 (m, 2H), 3.55 (t, J = 7.6 Hz, 2H), 1.49-1.46 (m, 2H), 1.29-1.34 (m, 8H), 0.99-0.96 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ165.2, 140.1, 134.2, 132.3, 130.5, 129.5, 128.7, 62.5, 32.3, 30.6, 29.7, 25.9, 23.1, 14.3.EI-MS: m/z 282.1 (M+H)$^+$.



6a : Yellow solid; mp: 135-137 ºC;^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01-7.94 (m, 2H), 7.69-7.59 (m, 2H), 2.66 (t, J = 6.2 Hz, 4H), 2.49 (t, J = 6.2 Hz, 4H), 2.28 (s, 3H);^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 136.5, 134.3, 131.6, 131.1, 128.7, 127.4, 55.5, 47.4, 43.3;EI-MS: m/z 266.1 (M+H)$^+$.



6b : Yellow solid;mp: 165-167 ºC;^{1}H NMR (400 MHz, DMSO-d_6) δ8.01-7.94 (m, 2H), 7.69-7.59 (m, 2H), 2.68 (d, J = 6.4 Hz, 8H), 2.21 (bs, 1H);^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 136.5, 134.3, 131.6, 131.1, 128.7, 127.4, 49.9, 46.8;EI-MS: m/z 252.07 $(M+H)^+$.



6c: Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ8.02-7.95 (m, 2H), 7.65-7.54 (m, 2H), 4.45 (t, J = 6.0 Hz, 1H), 3.25 (s, 6H), 2.97 (d, J = 6.0 Hz, 2H), 2.31 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 136.4, 134.3, 131.7, 131.1, 128.7, 127.3,106.5, 53.3, 41.1;EI-MS: m/z 271.08 $(M+H)^+$.

APPLICATIONS

The saccharin and its derivatives can be prepared inexpensive way.

CONCLUSIONS

In summary, saccharin derivatives could be readily prepared from inexpensive and readily available materials. Iodo and aldehyde derivatives also were prepared and well characterized by spectral data (NMR, MS).Investigation of the biological activities of these compounds is underway.

ACKNOWLEDGEMENTS

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