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Synthesis and antifungal activity of N-(alkyl/aryl)-2-(3-oxo-1,4-benzothiazin-2-yl)acetamide

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A series of N-(alkyl/aryl)-2-(3-oxo-1,4-benzothiazin-2-yl)acetamide have been synthesized by condensation of substituted amines with maleic anhydride (MA) followed by cyclization with *o*-aminothiophenol (*o*-ATP). All the compounds have been screened for their antifungal activity against *Tricophyton rubrum*, *Epidermophyton floccosum* and *Malassazia furfur*. In the primary screening, some of the compounds exhibited appreciable activity. The structures of the synthesized compounds **7a-z** have been established on the basis of elemental analysis and spectral data.

Key words: N-(alkyl/aryl)-2-(3-oxo-1,4-benzothiazin-2-yl)acetamide, *o*-ATP, maleic anhydride, amines

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Incidences of fungal infections have increased dramatically in the last few decades. The incidences of infection in hair, nails and the outer layer of epidermis are very common in India[1]. This type of infection is collectively known as Dermatophytoses and caused by dermatophytes (superficial fungi)[2,3]. Intact dry skin is an effective barrier against many diseases but aforementioned incidences of infections develop with fungal infections[4]. The increased intensity of these life threatening fungal infections and the development of resistance to the currently used antifungal agents warrant the search for novel, alternative chemical moieties. This encouraged us to synthesize compounds like N-(alkyl/aryl)-2-(3-oxo-1,4-benzothiazin-2-yl)acetamide. It has been previously reported that substituted acid/ester compounds containing benzothiazine[5-9] moiety exhibited prominent antifungal activity.

Due to the interesting activity of various substituted benzothiazines[10-13] as biological agents, they are the subject of considerable attention. The pharmaceutical importance of these compounds lies in the fact that they are effective as anti-inflammatory[14,15], anthelmintic[16-18], anti-fungal[18] and CNS depressants[18] (**Figure 1**).

Results and Discussion

N-(alkyl/aryl)-2-(3-oxo-1,4-benzothiazin-2-yl)acetamide **7a-z** was prepared by the condensation of the corresponding isomerized maleanillic ester **5a-z** with *o*-ATP in DMF solvent. The reaction mixture was allowed to reflux for 5 hr and the product was isolated by dumping the mixture into crushed ice. The starting isomerized maleanillic ester **5a-z** was prepared by a three-step process from substituted amines **1** and maleic anhydride **2**. Maleanillic acid **3a-z** was synthesized by the reaction of substituted amines **1** with maleic anhydride **2** in ether solvent at rt. Maleanillic ester **4a-z** was synthesized from **3a-z** by esterification with methanol in the presence of P_2O_5. Isomerized maleanillic ester **5a-z** was synthesized by isomerization of **4a-z** in the presence of aniline.

The synthesis is outlined in **Scheme I**. The characterization data of compounds **3a-y, 4a-y, 5a-y** and **7a-y** are given in **Tables I** and **II**.

Biological activity

Antifungal activity

The synthesized compounds **7a-z** in the concentration range 0.25-0.031 μmole/mL were tested for

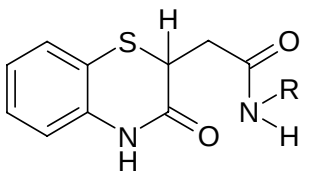
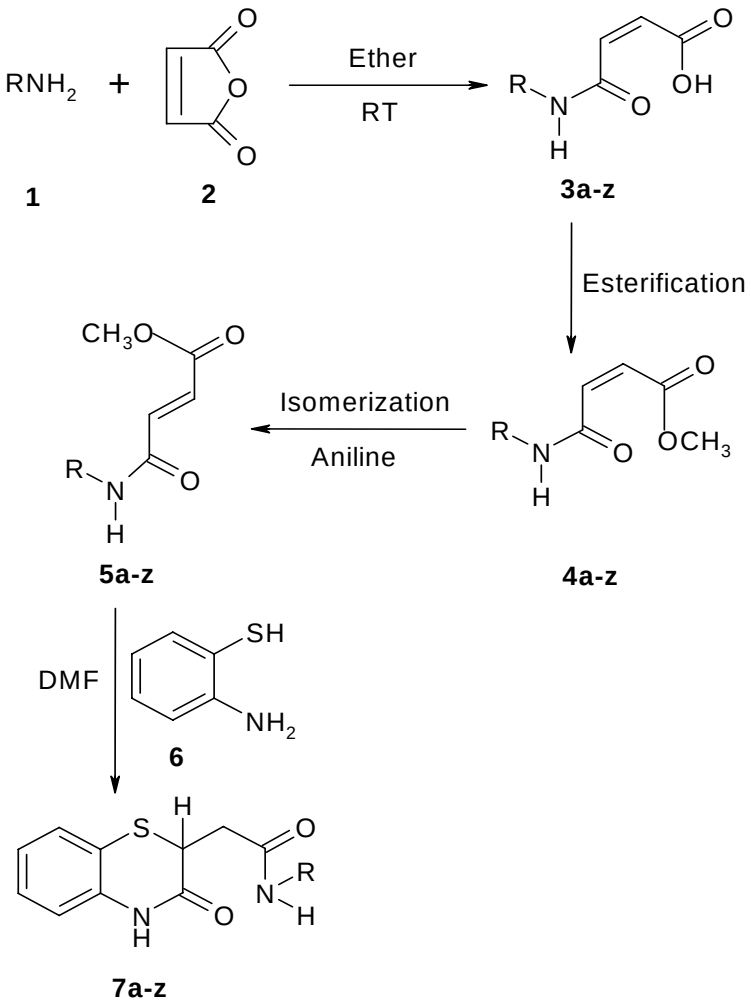


Figure 1



Scheme I

Table I − Characterization data of compounds **3a-y, 4a-y** and **5a-y**

Compd	R	Yield (%)			m.p.(°C)		
		Acid **3**	Ester **4**	I. Ester **5**	Acid **3**	Ester **4**	I. Ester **5**
a	$-CH_3$	79	46	50	135-40	153-56	121-23
b	$-C(CH_3)_3$	89	49	56	142-45	150-53	82-6
c	$-C_2H_5$	85	56	66	131-34	130-33	115-16
d	$-(CH_2)_3-CH_3$	94	56	64	77-80	96-8	56-8
e	$-CH_2-CH_2-OH$	86	54	67	121-23	125-27	112-13
f	$-C_6H_4$-4-OH	89	50	84	158-59	156-58	105-07
g	$-C_6H_4$-2-OH	94	49	70	168-72	138-40	102-06
h	$-C_6H_3$-3-Cl-4-OH	82	49	53	210-12	220-22	156-60
i	$-CH(CH_3)-CH_2-OH$	78	50	78	96-8	120-22	84-6
j	$-C_6H_3$-2-CH_3-3-NO_2	92	54	67	115-17	125-27	99-101
k	$-C_6H_4$-3-NO_2	79	56	76	120-21	145-47	102-04
l	$-C_6H_4$-4-NO_2	93	67	74	97-9	95-7	56-9
m	$-C_6H_4$-2-CH_3	96	49	59	120-22	55-7	96-9
n	$-C_6H_4$-3-CH_3	87	56	54	191-94	70-2	78-81

— *Contd*

Table I − Characterization data of compounds **3a-y, 4a-y** and **5a-y** — *Contd*

Compd	R	Yield (%)			m.p.(°C)		
		Acid **3**	Ester **4**	I. Ester **5**	Acid **3**	Ester **4**	I. Ester **5**
o	$-C_6H_4-4-CH_3$	73	58	74	98-100	111-12	89-91
p	$-C_6H_4-2-C_2H_5$	87	46	60	96-8	89-91	89-92
q	$-C_6H_4-2-Cl$	88	59	55	124-26	80-4	102-04
r	$-C_6H_4-3-Cl$	97	54	55	193-94	190-92	126-28
s	$-C_6H_4-4-Cl$	95	65	53	198-99	67-70	69-71
t	$-C_6H_2-2,4,5-Cl$	84	48	66	158-60	165-66	136-38
u	$-C_6H_4-2-OCH_3$	82	59	56	133-37	102-07	96-9
v	$-C_6H_4-3-OCH_3$	95	57	56	121-22	134-36	102-03
w	$-C_6H_4-4-OCH_3$	86	58	55	175-79	187-88	154-56
x	$-C_6H_{11}$	78	65	59	110-13	65-8	60-3
y	$-CH_2-C_6H_5$	85	56	66	131-34	130-33	115-16

Table II — Characterization data of compounds **7a-y**

Compd	R	Yield (%)	m.p. (°C)	R_f	Mol. formula	Found % (Calcd) C	H	N
7a	$-CH_3$	60	233-35	0.56	$C_{11}H_{12}N_2O_2S$	55.91 (55.89	5.17 5.17	11.86 11.86)
7b	$-C(CH_3)_3$	55	190-92	0.51	$C_{14}H_{18}N_2O_2S$	60.4 (60.6	6.52 6.53	10.0 10.1)
7c	$-C_2H_5$	83	180-82	0.54	$C_{12}H_{14}N_2O_2S$	57.8 (57.6	5.64 5.62	11.19 11.20)
7d	$-(CH_2)_3-CH_3$	69	188-90	0.60	$C_{14}H_{18}N_2O_2S$	60.4 (60.6	6.12 6.10	10.06 10.09)
7e	$-CH_2-CH_2-OH$	54	185-88	0.42	$C_{12}H_{14}N_2O_3S$	54.12 (54.15	5.30 5.29	10.52 10.51)
7f	$-C_6H_4-4-OH$	79	228-30	0.44	$C_{16}H_{14}N_2O_3S$	61.13 (61.16	4.49 4.50	8.91 8.93)
7g	$-C_6H_4-2-OH$	77	203-05	0.66	$C_{16}H_{14}N_2O_3S$	61.13 (61.11	4.49 4.48	8.91 8.90)
7h	$-C_6H_3-3-Cl-4-OH$	65	208-11	0.14	$C_{16}H_{13}N_2O_3SCl$	55.09 (55.10	3.76 3.74	8.03 8.02)
7i	$-CH(CH_3)-CH_2-OH$	67	206-08	0.54	$C_{13}H_{16}N_2O_3S$	55.70 (55.72	5.75 5.77	9.99 9.98)
7j	$-C_6H_3-2-CH_3-3-NO_2$	56	155-59	0.45	$C_{17}H_{15}N_3O_4S$	57.13 (57.11	4.23 4.24	11.76 11.78)
7k	$-C_6H_4-3-NO_2$	45	185-90	0.34	$C_{16}H_{13}N_3O_4S$	55.97 (55.95	3.82 3.80	12.24 12.26)
7l	$-C_6H_4-4-NO_2$	66	237-40	0.32	$C_{16}H_{13}N_3O_4S$	55.97 (55.96	3.82 3.81	12.24 12.25)
7m	$-C_6H_4-2-CH_3$	70	240-45	0.19	$C_{17}H_{16}N_2O_2S$	65.36 (65.38	5.16 5.17	8.97 8.95)
7n	$-C_6H_4-3-CH_3$	56	216-19	0.42	$C_{17}H_{16}N_2O_2S$	65.36 (65.37	5.16 5.17	8.97 8.96)
7o	$-C_6H_4-4-CH_3$	72	212-15	0.07	$C_{17}H_{16}N_2O_2S$	65.36 (65.35	5.16 5.18	8.97 8.98)
7p	$-C_6H_4-2-C_2H_5$	79	195-97	0.41	$C_{18}H_{18}N_2O_2S$	66.23 (66.25	5.56 5.55	8.58 8.57)

— *Contd*

Table II — Characterization data of compounds **7a-y** — *Contd*

Compd	R	Yield (%)	m.p. (°C)	R_f	Mol. formula	Found % (Calcd) C	H	N
7q	-C_6H_4-2-Cl	75	235-39	0.25	$C_{16}H_{13}N_2O_2SCl$	57.74 (57.76	3.94 3.93	8.42 8.41)
7r	-C_6H_4-3-Cl	76	215-18	0.43	$C_{16}H_{13}N_2O_2SCl$	57.74 (57.72	3.94 3.95	8.42 8.43)
7s	-C_6H_4-4-Cl	65	230-32	0.59	$C_{16}H_{13}N_2O_2SCl$	57.74 (57.75	3.94 3.93	8.42 8.43)
7t	- C_6H_2-2, 4,5-Cl	63	250-52	0.17	$C_{16}H_{11}N_2O_2SCl_3$	47.84 (47.85	2.76 2.74	6.97 6.96)
7u	-C_6H_4-2-OCH_3	76	182-85	0.42	$C_{17}H_{16}N_2O_3S$	62.18 (62.20	4.91 4.92	8.53 8.55)
7v	-C_6H_4-3-OCH_3	86	191-93	0.38	$C_{17}H_{16}N_2O_3S$	62.18 (62.19	4.91 4.90	8.53 8.55)
7w	-C_6H_4-4-OCH_3	79	188-90	0.35	$C_{17}H_{16}N_2O_3S$	62.18 (62.14	4.91 4.93	8.53 8.57)
7x	-C_6H_{11}	59	185-90	0.24	$C_{16}H_{20}N_2O_2S$	63.13 (63.14	6.62 6.63	9.20 9.18)
7y	-CH_2-C_6H_5	59	239-40	0.66	$C_{17}H_{16}N_2O_2S$	64.41 (64.40	4.73 4.74	9.39 9.40)

Mobile Phase: 8:2 (Chloroform:Methanol)

antifungal activity against *Tricophyton rubrum*, *Epidermophyton floccosum* and *Malassazia furfur* by turbidimetric method[2]. For comparison, ketoconazole was used as a standard. For screening, synthesized compounds were grouped using combinatorial chemistry **(Tables III** and **IV)**.

Results are presented in **Tables V, VI** and **VII**.

Experimental Section

Melting points of all the compounds were determined in open capillary tubes and are uncorrected. Thin layer chromatography was performed using silica gel coated on a glass plate and spots were visualized by exposure to iodine vapor. IR spectra were recorded on a Shimadzu IR spectrophotometer using Nujol. ^{1}H NMR spectra were recorded in $CDCl_3$/acetone-d_6 on a FX 90Q FT NMR spectrometer using TMS as internal standard (chemical shifts in δ, ppm).

Maleanillic acids 3a-z. To the solution of maleic anhydride (9.8 g, 0.1 mole) in diethyl ether (40 mL), a solution of aniline (9.3 g, 0.1 mole) in diethyl ether (40 mL) was added. The reaction mixture was stirred at rt for 5 min. The precipitate was filtered, washed with ether (2 × 30 mL) and purified by recrystallization from acetone-petroleum ether to get the compound **3z**. Yield 95%, m.p. 201-03ºC. The other compounds **3a-y** were also prepared in a similar way by the reaction of **2** with various amines **1**.

Table III — Grouping of synthesized compounds **7a-z** using combinatorial chemistry

Set	Compd
R_1	**7a, 7b, 7c, 7d**
R_2	**7e, 7f, 7g, 7h, 7i**
R_3	**7j, 7k, 7l**
R_4	**7m, 7n, 7o, 7p**
R_5	**7q, 7r, 7s, 7t**
R_6	**7u, 7v, 7w**
R_7	**7x, 7y, 7z**

Table IV — Grouping of active compounds found after preliminary screening using combinatorial chemistry

Set	Compd *Epidermophyton floccosum*	*Tricophyton rubrum*	*Malassazia furfur*
S_1	**7j, 7x**	**7a, 7x**	**7a, 7x**
S_2	**7k, 7y**	**7b, 7c, 7y**	**7b, 7c, 7y**
S_3	**7l, 7z**	**7d, 7z**	**7d, 7z**

Maleanillic esters 4a-z. To ice-cold methanol (60 mL), phosphorus pentaoxide (8.5 g, 0.06 mole) was added in portions with stirring and the temperature was kept below 10ºC. To the resulting solution, **3z** (5.7 g, 0.03 mole) was added in one portion and was mixed gently. It was then refluxed for 6 hr on a water bath. Excess methanol was distilled out under reduced

Table V — Antifungal activity data of compounds set R_1-R_7

	Concentration of compounds (1 μmole/mL) required for inhibition											
	Epidermophyton floccosum				*Tricophyton rubrum*				*Malassazia furfur*			
Set	0.25	0.125	0.062	0.031	0.25	0.125	0.062	0.031	0.25	0.125	0.062	0.031
R_1	(-)	(+)	(+)	(+)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(+)
R_2	(-)	(+)	(+)	(+)	(-)	(+)	(+)	(+)	(-)	(+)	(+)	(+)
R_3	(-)	(-)	(-)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
R_4	(+)	(+)	(+)	(+)	(-)	(+)	(+)	(+)	(-)	(+)	(+)	(+)
R_5	(-)	(+)	(+)	(+)	(-)	(+)	(+)	(+)	(-)	(+)	(+)	(+)
R_6	(-)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(-)	(+)	(+)	(+)
R_7	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)
K	(-)	(-)	(+)	(+)	(-)	(-)	(+)	(+)	(-)	(-)	(+)	(+)

Table VI— Antifungal activity data of compounds set S_1-S_3

	Concentration of compounds (1 μmole/mL) required for inhibition											
	Epidermophyton floccosum				*Tricophyton rubrum*				*Malassazia furfur*			
Set	0.25	0.125	0.062	0.031	0.25	0.125	0.062	0.031	0.25	0.125	0.062	0.031
S_1	(-)	(+)	(+)	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(+)
S_2	(-)	(-)	(-)	(+)	(-)	(+)	(+)	(+)	(-)	(+)	(+)	(+)
S_3	(-)	(+)	(+)	(+)	(-)	(+)	(+)	(+)	(-)	(+)	(+)	(+)
K	(-)	(-)	(+)	(+)	(-)	(-)	(+)	(+)	(-)	(-)	(+)	(+)

(-) Indicates inhibition of growth
(+) Indicates presence of growth
K-Ketoconazole

Table VII — Antifungal activity data of compounds **7a, 7k, 7x** and **7y**

	Concentration of compounds (1 μmole/mL) required for inhibition			
	Epidermophyton floccosum			
Compd	0.25	0.125	0.062	0.031
7 k [-(C_6H_4)-3-NO_2]	(-)	(-)	(-)	(+)
7 y [-C_6H_5]	(-)	(-)	(+)	(+)
	Tricophyton rubrum			
Compd	0.25	0.125	0.062	0.031
7 a [-CH_3]	(-)	(-)	(+)	(+)
7 x [-C_6H_{11}]	(-)	(-)	(-)	(+)
	Malassazia furfur			
Compd	0.25	0.125	0.062	0.031
7 a [-CH_3]	(-)	(-)	(-)	(+)
7 x [-C_6H_{11}]	(-)	(-)	(+)	(+)
K	(-)	(-)	(+)	(+)

(-) Indicates inhibition of growth
(+) Indicates presence of growth
K-Ketoconazole

pressure. The resulting residue was poured into crushed ice, filtered and purified by recrystallization from ethanol to get the compound **4z**. Yield 51%, m.p. 196-99ºC. The other compounds **4a-y** were also prepared in a similar way from **3a-y**.

Isomerised maleanillic esters 5a-z. To the solution of **4z** (4.1 g, 0.02 mole) in absolute ethanol (40 mL), a solution of redistilled aniline (0.93 g, 0.01 mole) was added. The resulting mixture was refluxed on a steam bath for 3 hr. The precipitate was filtered, washed with dil. HCl (10 mL) and purified by recrystallization from ethanol to get the compound **5z**. Yield 63%, m.p. 159-61ºC. The other compounds **5a-y** were also prepared in a similar way from **4a-y**.

N-(alkyl/aryl)-2-(3-oxo-1,4-benzothiazin-2-yl)acetamide 7a-z. To the solution of **5z** (10.2 g, 0.05 mole) in DMF (100 mL), a solution of *o*-ATP (6.25 g, 0.05 mole) in DMF (20 mL) was added. The resulting mixture was refluxed for 5 hr. The solution was cooled and poured into crushed ice. The solid that separated out was filtered, washed with water and purified by recrystallization from ethanol to get the compound **7z**. Yield 75%, m.p. 262-66ºC. Anal. Calcd for

$C_{16}H_{14}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97, Found: C, 65.34; H, 5.12; N, 8.96%; IR (Nujol): 3345 (NH), 1635 (NHCO), 2560 (S-H), 1760 cm^{-1} (C=O); ^1H NMR (for **7k**): δ 2.9 (m, 2H, $-CH_2CO$), 4.6 (m, 1H, S-CH), 7.4 (m, 8H, ArH), 9.8 (bs, 1H, NH), 10.8 (bs, 1H, NH); ^1H NMR (for **7r**): δ 2.8 (m, 2H, $-CH_2CO$), 4.3 (m, 1H, S-CH), 7-7.7 (m, 8H, ArH), 9.6 (bs, 1H, NH), 10.3 (bs, 1H, NH). The other compounds **7a-y** were also prepared in a similar way from **5a-y**.

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