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Synthesis and antimicrobial activity of some novel heterocycles containing thiazole, oxazole, thiazine, oxazine and triazole moiety

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Abstract

Indandione 1 was brominated to yield 2-bromoIndandione 2 which on further reacted with substituted thiocarbamides, carbamides, 2-aminothiophenols, 2-aminophenol and triazoles to furnished 3-substituted aniline-2-thia-4-aza-6,7-benzo-8-oxo-bicyclo [3.3.0]-1(5),3-octadiene 3, 3-substituted aniline-2-oxa-4-aza-6,7-benzo-8-oxo-bicyclo [3.3.0]-1(5),3-octadiene 4, 2-Thia-5-aza-9-oxo-3,4-(3'-substituted) benzo-7,8-benzo-bicyclo [4.3.0]-1(6) nonene 5, 2-oxa-5-aza-9-oxo-(3, 4)-(7, 8)-dibenzo-bicyclo [4.3.0]-1(6) nonene 6, 3-substituted-(1,2,4) triazolo [4,5-b] [indeno (2,3-e)]-1,3,4-thiadiazine 7 respectively.

Keywords: Monobromoindandione; Thiocarbamide; Carbamide; 2-Aminothiophenol; 2-Aminophenol; Triazole.

1. Introduction

Heterocyclic compounds constitute the largest family of organic compounds, regardless of structure and functionality. Heterocyclic compounds are of particular interest in medicinal chemistry and this has catalyzed the discovery and development of many new heterocyclic compounds. In the literature, the compounds bearing thiazole and oxazole moiety have been found to possess antibacterial [1], antitubercular [2] and anti-inflammatory [3] activity. Similarly heterocycles containing thiazine and oxazine moiety are well known for their diverse biological activities and play a key role as anti-psychotic [4], antiviral [5] and anti-microbial agents [6]. Fused *s*-triazoles and their derivatives have been investigated for their potential pharmacological properties such as antifungal [7], antidepressant [8] and plant growth regulators [9]. In view of the biological potential of the above pharmacophore, syntheses of various derivatives have been undertaken.

2. Experimental

2.1. Methods and Analysis

All chemicals were supplied by E. Merck (Germany) and S. D. Fine Chemicals (India). Melting points of all synthesized compounds were determined in open capillary tubes using

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Veego VMP-1 melting point apparatus and have been expressed in °C. The progress of the reaction was monitored in-situ by a thin layer chromatography on silica gel coated aluminium plates as adsorbent and UV light as visualizing agent. IR spectra in KBr pellets were recorded on Perkin-Elmer spectrophotometer in the range of 4000-400 cm^{-1}. ^1H NMR spectra were obtained by using Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard. C, H, N analyses were performed on Carlo Erba 1108 (C H N) Elemental Analyzer.

2.2. General procedure and spectral analysis of representative compounds

2.2.1. Synthesis of 2-bromoIndandione, 2

Indandione **1** (0.01 mole) was dissolved in 10 mL of glacial acetic acid. A solution of bromine (0.01 mole) in glacial acetic acid was added dropwise with continuous stirring in presence of UV light. The stirring was continued for One hour. The reaction mixture was quenched into ice-cold water and the product was separated out, filtered and washed with cold water. The product was purified by recrystallization from ethanol to give 2-bromo-Indandione **2**, yield 86%, m.p.98-101°C.

2.2.2. 3-(substituted)-imino-2-thia-4-aza-6,7-benzo-8-oxo-bicyclo[3.3.0]-1(5),3-octadiene, 3a-f

A mixture of compound **2** (0.01 mole) and substituted thiocarbamide (0.01 mole) in ethanol (20 mL) was refluxed in the presence of dimethylformamide (DMF) (0.02 mole) for about 4 to 5 hours. The progress of reaction was monitored on Thin Layer Chromatography (TLC). Upon completion of reaction, the reaction mixture was quenched into crushed ice. The precipitated product was filtered, washed with water and crystallized from ethanol to give thiazoles **3a-f**.

2.2.3. 3-(methoxy)-imino-2-thia-4-aza-6,7-benzo-8-oxo-bicyclo[3.3.0]-1(5),3-octadiene(3d)

m.p. 210-213°C, Yield = 87%
IR (KBr) IR: 3168, 1276 cm^{-1}.
^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 3.9 (s, 3H, OCH_3), 7.2 – 8.2 (m, 8H, ArH), 9.8 (s, 1H, NH).
^{13}C NMR (500 MHz, DMSO-d_6, ppm): 55.4 (OCH_3), 114.2-120.7 (C=C),
121.7-139.9 (Ar C), 156.3 (C=N), 182.7 (C=O).
Calcd for $C_{17}H_{12}N_20_2S$: C,66.22;H,3.92;N,9.08%.Found C,66.32;H,4.02,N,9.12%.

2.2.4. 3-(substituted)-imino-2-oxa-4-aza-6,7-benzo-8-oxo-bicyclo[3.3.0]-1(5),3-octadiene, 4a-f

A mixture of compound **2** (0.01 mol) and substituted carbamides (0.01 mol) in ethanol (20 ml) was refluxed in the presence of dimethylformamide (DMF) (0.02 mol) for about four to five hours. The progress of reaction was monitored on Thin Layer Chromatography (TLC). Upon completion of reaction, the reaction mixture was quenched into crushed ice. The precipitated product was filtered, washed with water and purified by recrystallization from ethanol to give Oxazoles. **4a-f**.

2.2.5. 3-(methyl)-imino-2-oxa-4-aza-6, 7-benzo-8-oxo-bicyclo [3.3.0]-1(5),3-octadiene (4f)

m.p. 180-184 °C, Yield = 89%
IR (KBr) IR: 3173, 1666 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.22 (s, 3H, CH3), 7.2 – 8.2 (m, 8H, ArH), 9.85 (s, 1H, NH).
^{13}C NMR (500 MHz, DMSO-d_6, ppm): 23.91 (OCH3), 115.1-119.4(C=C), 122.4-131.7 (Ar C), 152.6 (C=N), 179.5(C=O).
Calcd for $C_{17}H_{12}N_20_2$: C,73.90;H,4.38;N,10.14%.Found C,73.84;H,4.32,N,10.19%.

2.2.6. 2-Thia-5-aza-9-oxo-3,4-(substituted)benzo-7,8-benzo-bicyclo [4.3.0]-1(6)nonene,5a-c

An equimolar mixture of compound **2** (0.01 mole) and substituted aminothiophenol (0.01 mole) in ethanol (20 mL) was refluxed in the presence of dimethylformamide (DMF) (0.02 mole) for about four to five hours. The progress of reaction was monitored on Thin Layer Chromatography (TLC). Upon completion of reaction, the reaction mixture was quenched into crushed ice. The precipitated product was filtered, washed with water and purified by recrystallization from ethanol to give Thiazines. **5a-c.**

2.2.7. 2-Thia-5-aza-9-oxo-3, 4-benzo-7, 8-benzo-bicyclo [4.3.0]-1(6) nonene(5a)

m.p. 146-148 °C, Yield = 89%
IR (KBr) IR: 3290, 1660 cm^{-1}.
^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 7.2 – 8.2 (m, 8H, ArH), 9.8(s, 1H, NH).

2.2.8. 2-Thia-5-aza-9-oxo-3, 4-(3'-methyl) benzo-7,8-benzo-bicyclo [4.3.0]-1(6) nonene (5c)

m.p. 120-124 °C, Yield = 82%
IR (KBr) IR: 3360, 1680 cm^{-1}.
^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.48 (s, 3H, CH_3), 7.2 – 8.2 (m, 8H, ArH), 10.4 (s, 1H, NH).
^{13}C NMR (500 MHz, DMSO-d_6, ppm): 23.91 (CH3), 118.2-120.3(C=C), 121.8-135.6 (Ar C), 180.5(C=O).
Calcd for $C_{16}H_{11}N0S$: C,72.43;H,4.18;N,5.28%.Found C,72.34;H,4.23,N,5.19%.

2.2.9. 2-oxa-5-aza-9-oxo-(3,4)-(7,8)-dibenzo-bicyclo [4.3.0]-1(6) nonene (6)

An equimolar mixture of compound **2** (0.01 mole) and aminophenol (0.01 mole) in ethanol (20 mL) was refluxed in the presence of dimethylformamide (DMF) (0.02 mole) for about four to five hours. The progress of reaction was monitored on Thin Layer Chromatography (TLC). Upon completion of reaction, the reaction mixture was quenched into crushed ice. The precipitated product was filtered, washed with water and purified by recrystallization from ethanol to yield **6**.

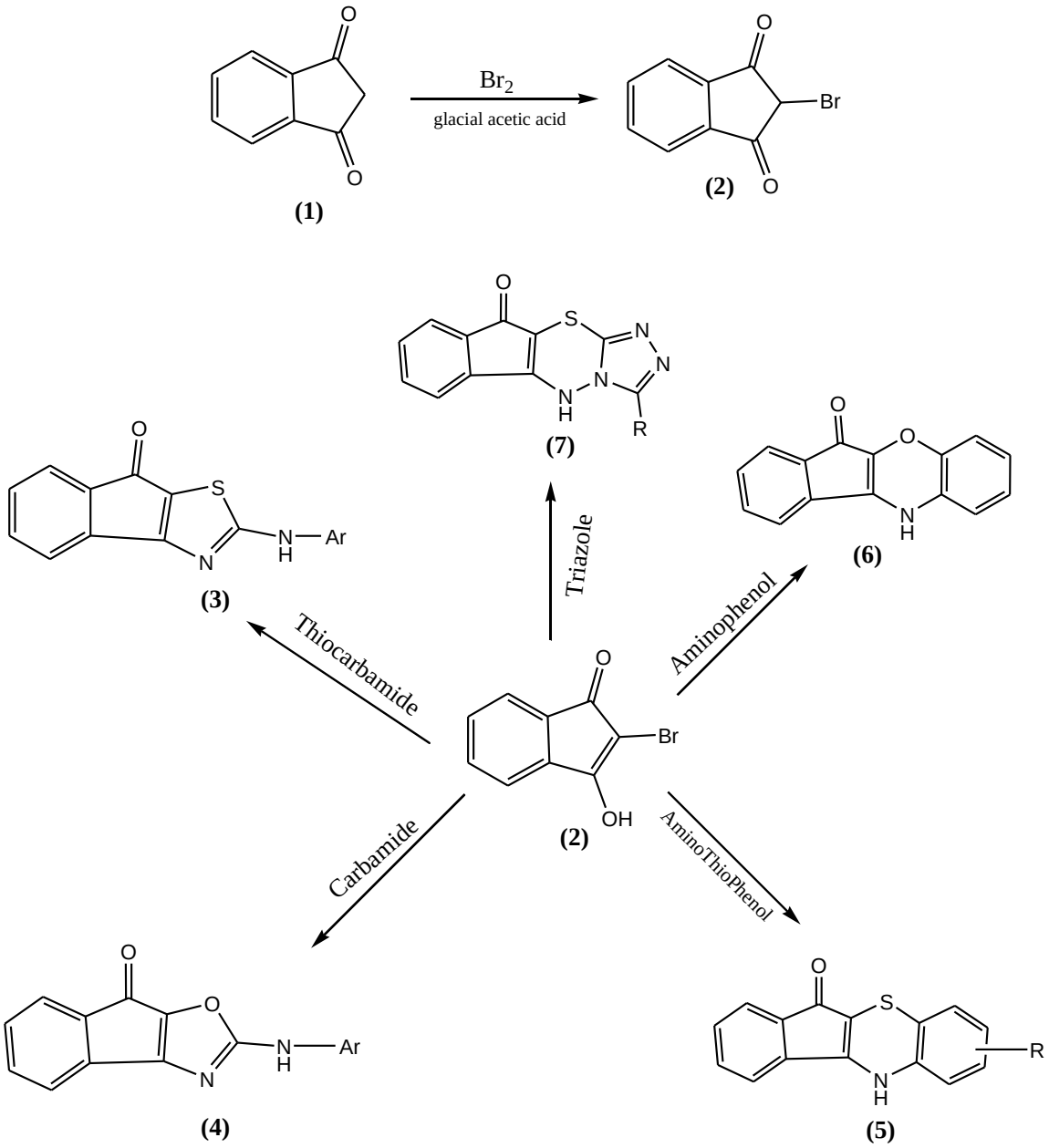
2.2.10. 3-substituted-(1,2,4) triazolo [4,5-b] [indeno (2,3-e)]-1,3,4-thiadiazine, 7a-c

An equimolar mixture of compound **2** (0.01 mole) and substituted Triazole (0.0 mole) in ethanol (20 mL) was refluxed in the presence of dimethylformamide (DMF) (0.02 mole) for about four to five hours. The progress of reaction was monitored on Thin Layer Chromatography (TLC). Upon completion of reaction, the reaction mixture was quenched into crushed ice. The precipitated product was filtered, washed with water and purified by recrystallization from ethanol to yield **7a-c**.

2.2.11. 3-methyl-(1,2,4) triazolo [4,5-b] [indeno (2,3-e)]-1,3,4-thiadiazine(7b)

m.p. 201-203 °C, Yield = 87%

IR (KBr): IR: 3153, 1730cm^{-1}.
^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.4(s, 3H, CH_3), 7.0 – 8.5 (m, 4H, ArH), 8.9 (s, 1H, NH).
^{13}C NMR (500 MHz, DMSO-d_6, ppm): 13.67 (CH_3), 122.5- 124.3 (C=C), 126.8-137.9 (Ar C), 148.5 (C=N), 156.5 (C=N), 168.4(C=O).
Calcd for $C_{12}H_8N_40S$: C,56.24;H,3.15;N,21.86%.Found C,56.34;H,3.12,N,21.79%.



Reaction condition : Alcohol/Reflux for 4-5Hrs/DMF

3a:Ar:H
3b: Ar:C_6H_5
3c: Ar:4-Cl-C_6H_4
3d: Ar:4-OCH_3-C_6H_4
3e: Ar:3-Cl-C_6H_4
3f:Ar:4-CH_3-C_6H_4

4a: Ar:H
4b: Ar:C_6H_5
4c: Ar:4-Cl-C_6H_4
4d: Ar:4-OCH_3-C_6H_4
4e: Ar:4-NO_2-C_6H_4
4f: Ar:4-CH_3-C_6H_4

5a:R:4-H
5b:R:4-Cl
5c:R:4-CH_3

7a:R: H
7b:R: CH_3
7c:R:C_2H_5

Scheme 1. Synthesis of compounds 3, 4, 5, 6 and 7.

2.3 Antimicrobial Evaluation

The newly synthesized compounds were tested for their antimicrobial activity against the following microorganisms: (a) Gram-negative: Escherichia coli, Pseudomonas putide; (b) Gram-positive: Bacillus subtilis, Streptococcus lactis; (c) Fungi: Aspergillus niger, Penicillium sp.; (d) Yeast: Candida albicans. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method [14]. The compounds were tested at a concentration of 100 µg mL^{-1}. The zone of inhibition was measured in mm and compared with reference standard ampicillin trihydrate (100 µg mL^{-1}). The compounds tested have displayed good activity towards Gram positive bacteria, but were less active against Gram-negative bacteria. The activities of representative compounds are reported in Table 1.

Table 1
Antimicrobial activities of some newly synthesized compounds.

Comound	Inhibition Zone (mm)						
	Gram-negative		Gram-positive		Fungi		Yeast
	E.coli	*P.Putide*	*B.Subtilis*	*S.lactis*	*A.niger*	*P.Sp.*	*C.Albicans*
3d	17	15	18	21	12	10	5
4f	16	16	17	21	10	10	5
5a	15	14	18	19	8	8	5
5c	18	19	19	20	8	8	5
7b	13	18	17	20	0	0	0
Ampicilin®	24	20	19	22	24	14	14

E.coli. = Escherichia coli; P.Putide = Pseudomonas Putide; B. Subtilis = Bacillus Subtilis; S. lactis = Sterptococcus lactis; A. niger = Aspergillus niger; P. Sp. = Penicillium Sp; C. Albicans = candida Albicans.
The sensitivity of microorganisms to the tested compounds is identified in the following manner*;
Highly Sensitive = Inhibition zone: 15-20 mm
Moderately Sensitive = Inhibition zone: 10-15 mm
Slightly Sensitive = Inhibition zone: 5-10 mm
Not Sensitive = Inhibition zone: 0 mm
* Each result represents the average of triplicate readings.

3. Result and Discussion

The synthesis of 2-bromo-Indandione 2 was achieved from Indandione 1 using bromine in glacial acetic acid. The title compounds 3-(substituted)-imino-2-thia-4-aza-6,7-benzo-8-oxo-bicyclo[3.3.0]-1(5), 3-octadiene 3a-f, 3-(substituted)-imino-2-oxa-4-aza-6,7-benzo-8-oxo-bicyclo[3.3.0]-1(5), 3-octadiene 4a-f, 2-Thia-5-aza-9-oxo-3,4-(3'-substituted) benzo-7,8-benzo-bicyclo [4.3.0]-1(6) nonene 5a-c, 2-oxa-5-aza-9-oxo-(3,4)-(7,8)-dibenzo-bicyclo [4.3.0]-1(6) nonene 6 and 3-substituted-(1,2,4) triazolo [4,5-b] [indeno (2,3-e)]-1,3,4-thiadiazine 7a-c were synthesized by reacting bromo compound 2 with substituted thiocarbamides [10], carbamides [11], 2-aminothiophenols [12],[13], 2-aminophenol and Triazoles respectively in presence of dimethylformamide (DMF) as a catalyst and ethanol as a solvent (Scheme 1). The Physical Characterization is given in Table 2.

Table 2
Physical characterization data of compounds 3, 4, 5, 6 and 7.

Compounds	Ar/R	Mol. Formula	m.p. (°C)	Yields (%)
3a	H	$C_{10}H_6ON_2S$	>260	88
3b	C_6H_5	$C_{16}H_{10}ON_2S$	245-247	89
3c	4-Cl-C_6H_4	$C_{16}H_9ON_2SCl$	220-223	92
3d	4-OCH_3-C_6H_4	$C_{17}H_{12}O_2N_2S$	210-213	87
3e	3-Cl-C_6H_4	$C_{16}H_{10}ON_2S$	198-202	89
3f	4-CH_3-C_6H_4	$C_{17}H_{12}ON_2S$	228-231	87
4a	H	$C_{10}H_6O_2N_2$	178-180	89
4b	C_6H_5	$C_{16}H_{10}O_2N_2$	172-174	82
4c	4-Cl-C_6H_4	$C_{16}H_9O_2N_2Cl$	164-166	81
4d	4-OCH_3-C_6H_4	$C_{17}H_{12}O_3N_2$	155-159	87
4e	4-NO_2-C_6H_4	$C_{16}H_{10}O_4N_3$	207-208	86
4f	4-CH_3-C_6H_4	$C_{17}H_{12}O_2N_2$	180-184	89
5a	H	$C_{15}H_9NOS$	146-148	89
5b	Cl	$C_{15}H_8NOSCl$	145-147	84
5c	CH_3	$C_{16}H_{11}NOS$	120-124	82
6	H	$C_{15}H_9NO_2$	187-189	91
7a	H	$C_{11}H_6N_4OS$	215-217	81
7b	CH_3	$C_{12}H_8N_4OS$	201-203	87
7c	C_2H_5	$C_{13}H_{10}N_4OS$	229-231	84

4. Conclusion

A number of new bicyclic compounds were prepared in moderately yield, some representative compounds were further screened for their antimicrobial activity which have showed good activity against gram positive as well as gram negative bacteria.

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