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A Comparison on Microwave and Ultrasound Accelerated Synthetic Route to Dihydropyrimidinones Catalyzed by Sulfanilic Acid in Water

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Abstract: 3,4-Dihydropyrimidin-2(1H)-ones, named as Biginelli compounds, are known to exhibit a wide range of biological activities such as antiviral, antitumor, antibacterial and anti-inflammatory actions. More recently, were shown as antihypertensive agents. A simple and green chemical procedure for the synthesis of dihydropyrimidinones under either microwave irradiation or the influence of ultrasonic radiation in the presence of a catalytic amount of sulfanilic acid in water as a green and benign solvent, is described. These methods provide an efficient and much improved modification of the original Biginelli reaction, in terms of high yields and short reaction times.

Key words: dihydropyrimidinones, sulfanilic acid, water, ultrasound.

INTRODUCTION

Recently, dihydropyrimidines (DHPMs) and their derivatives have attracted considerable interest because of their wide spectrum pharmacological activities such as antiviral, antihypertensive and antineoplastic effects (Kappe, C.O., 2000; Ghorab, M.M., 2000; Holla, B.S., 2004). They are the basis of several important drugs (e.g. Minoxidil and Tegafur Figure 1).

Minoxidil
(antihypertensive)

Tegafur
(anti-inflammatory)

Fig. 1:

Microwave and ultrasound-accelerated chemical reactions are well-known and proceed smoothly to provide improved yields and increased selectivities (Gaplovsky, A., 2000; Suslick, K.S., 1988; Rajagopal, R., 2002; Deshmukh, R.R., 2001). Therefore, microwave and ultrasound irradiations have been established as important techniques in organic syntheses (Mandhane, P.G., 2010; Joshi, R.S., 2010).

The zwitter ionic property of sulfanilic acid (Lenarsic, R., 1999) prompted us to use it as acid catalyst. In continuation to our interest in synthesis of heterocyclic compounds under ultrasonic radiation (Al-Zaydi, K.M., 2010; Al-Zaydi, K.M., 2010; Al-Zaydi, K.M., 2009; Hu, E.H., 1998), herein, we are reporting sulfanilic acid as an organic catalyst for greener synthesis of 3,4-dihydro-pyrimidin-2-(1H)-ones in water as a green solvent under microwave and sonication conditions.

RESULTS AND DISCUSSION

The syntheses of dihydropyrimidinones were carried out in three different conditions, using sulfanilic acid as catalyst in water.

To outline the role of microwave or ultrasound, the syntheses of dihydropyrimi-dinones were investigated under conventional heating, microwave irradiation or ultrasound radiation. In all reactions it was found that the use of MW or ultrasound irradiation leads to a higher yield.

First, the efficacy of the catalyst (sulfanilic acid) was tested for the reaction of equimolar amounts of benzaldehyde, ethylacetoacetate and urea under the three different conditions, reflux, microwave or ultrasound irradiation in water as solvent (Table 1). Control experiment without using the catalyst did not yield any product. Then the reaction was performed in the presence of 10 mol% of sulfanilic acid to afford in each case the same product (pyrimidinones 4a–d) in good to excellent yields (Scheme 1).

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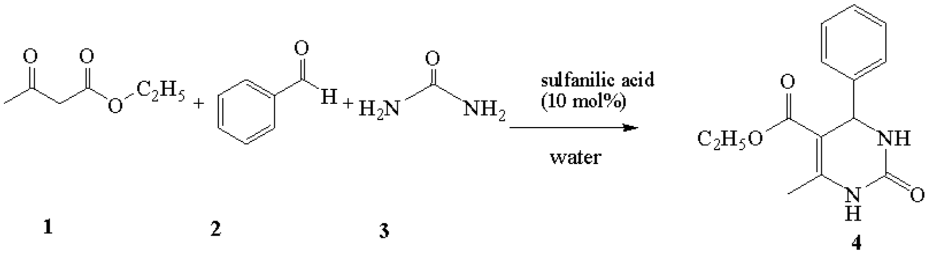


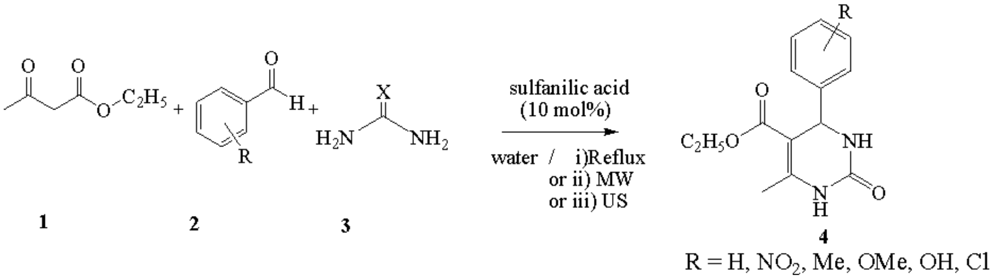
Scheme 1:

Table 1 shows the yield and time of the reaction of benzaldehyde, ethylacetoaceacetate and urea in the presence of different concentrations of the catalyst for the synthesis of **4a** in absence or presence of microwave or ultrasound irradiation.The results showed that 5 mol % of catalyst were also efficient in this reaction at the expense of reaction time: 5min, 82% yield and 3 h, 91% under microwave and sonication conditions respectively.

Table 1: Optimization of reaction conditions and the concentration of sulfanilic acid for the synthesis of **4.**

Mol % of sulfanilic acid	Classical heating		MW		US	
	Yield (%)	Time (h)	Yield (%)	Time (m)	Yield (%)	Time (h)
0	-	6	10	5	trace	6
2.5	-	6	23	5	12	6
5	-	6	82	5	91	3
10	trace	6	94	5	96	2
15	10	6	94	5	97	2
20	10	6	94	5	97	2

To study the generality of this process, a variety of substituted aromatic aldehydes, carrying either electron-donating or -withdrawing substituent, were examined. The effect of substituent on the aromatic ring did not show strongly obvious effects in terms of yields under the same reaction conditions. (Scheme 2, Table 2).



Scheme 2:

Using microwave or sonication condition not only provides an excellent yield of the pyrimidinones, *via* complete conversion, but also avoids the use of hazardous acids or bases and harsh reaction conditions in addition to the use of inexpensive catalyst under mild conditions and experimental operational ease.

Generally, yields of compound **4** afforded under sonication conditions are slightly higher than those obtained under microwave irradiation.

Pyrimidinones **4** were identified by their analytical and spectroscopic data in addition to m.p. determination and mixed m.p. with authentic samples.

Conclusion:

In conclusion, we have prepared 3,4-dihydro-pyrimidin-2(1H)-ones in water *via* Biginelli reaction using different concentration of sulfanilic acid as a catalyst by three methods, reflux, microwave and sonication. The yields obtained by the latter two methods are better and also with the use of very inexpensive catalyst, environmentally benign solvent and easy work-up are the advantageous aspects of the present method.

Table 2: Synthesis of different dihydropyrimidinones in presence of 10% mol of sulfanilic acid as a catalyst under different experimental conditions.

Entry	R	X	Product	Conventional method		Microwave irradiation		Ultrasound radiation	
				Time (h)	Yield/ref (%)	Time (min)	Yield/ref (%)	Time (min)	Yield/ref (%)
1	H	O	4a	6	trace	5	94	100	96
2	4-Me	O	4b	6	10	5	90	120	92
3	4-MeO	O	4c	6	12	2	94	90	98
4	4-HO	O	4d	6	9	4	90	120	93
5	3-HO	O	4e	8	8	5	68	120	74
6	3-Cl	O	4f	8	6	5	71	120	76
7	4-Cl	O	4g	6	8	3	91	110	94
8	4-N O_2	O	4h	6	12	4.5	92	95	96
9	H	S	4i	6	Trace	5	92	120	96
10	4-Me	S	4j	6	10	5	89	120	93
11	4-MeO	S	4k	6	10	5	94	120	97
12	4-Cl	S	4l	8	8	3.5	88	120	92
13	4-N O_2	S	4m	6	11	5	91	95	97

Experimental:

All melting points were measured on a Gallenkamp melting-point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO-d6). Chemical shifts were related to TMS. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses was carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Microwave irradiation was carried out by a domestic microwave oven (2450 MHz, 800 W) under atmospheric pressure. Sonication was performed by Fisher sonicator (with a frequency of 20 kHz and a nominal power 600 W). The reaction tube was located in the maximum energy area in it; where the surface of reactants (reaction vessel) is slightly lower than the level of the water

General Experimental Procedure for the Synthesis of 3,4-dihydropyrimidin-ones 4 in Water:

Method A:

Under Classical Heating Condition:

Reaction of benzaldhyde, ethylacetoaceacetate and urea in absence (or presence of catalytic amount of sulfanilic acid):

A mixture of benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (2 mmol) and sulfanilic acid (0-20 % mol, Table 1) in 25 ml water was refluxed for a suitable time till the reaction was completed (monitoring by TLC). The crude product which precipitated on cooling was filtered and recrystallized from EtOH to give pure crystals of pyrimidinones **4**.

Method B:

A 10 ml Pyrex tube was charged with a mixture of benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (2 mmol) and sulfanilic acid (0-20 % mol, Table 1) in 1 ml of water. The reaction mixture was subjected to microwave irradiation for a suitable time till the reaction was completed (monitoring by TLC). The solid material was filtered and the precipitate washed and recrystallized from EtOH to give pure crystals of pyrimidine **4**.

Method C:

A 10 ml Pyrex tube was charged with a mixture of benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (2 mmol) and sulfanilic acid (0-20 % mol, Table 1) in 1 ml of water. The reaction mixture was sonicated at room temperature for suitable time till the reaction was completed (monitoring by TLC). The solid material was filtered and the precipitate washed with water (2 mL) and recrystallized from EtOH to give pure crystals of pyrimidinones **4**.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4a):

Mp 203-204°C[14];IR (KBr) cm^{-}1 = 3249 and 3119 (N–H str.), 1698 and 1648 (C=O str.); ^{1}H NMR: δ=8.91(s, 1H, NH), 7.89(s, 1H, NH), 7.33(m, 5H, C_6H_5), 5.11(s, 1H, CH), 4.06(q, J = 6.8 Hz, 2H, O$\boldsymbol{CH_2}$$CH_3$), 2.21(s, 3H, CH_3), 0.99(t, J = 6.8 Hz, 3H, $OCH_2$$\boldsymbol{CH_3}$)

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimi-din-2(1H)-one (4b):

Mp 215-216°C[14]; : IR (KBr) cm^{-1}, 3242 and 3121 (N–H str.), 1694 and 1641 (C=O str.) ; ^{1}H NMR: δ=9.27 (s, 1H, NH), 7.78(s, 1H, NH), 7.03(2d, 4H, C$_6$H$_4$), 5.11(s, 1H, CH), 3.95(q, *J* = 7.2 Hz, 2H, O$\mathbf{CH_2}$CH$_3$), 2.19 (s, 3H, C$_6$H$_5$-$\mathbf{CH_3}$), 1.10 (t, *J* = 7.2 Hz, 3H, OCH$_2$$\mathbf{CH_3}$).

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimi-din-2(1H)-one (4c):

Mp 200-202°C[14], IR (KBr) cm^{-}1 = 3251 and 3108 (N–H str.), 1711 and 1652 (C=Ostr.); ^{1}H NMR: δ=10.01(s, 1H, NH), 7.72 (s, 1H, NH), 7.19-6.88(2d, 4H, C$_6$H$_4$), 5.09(s, 1H, CH), 3.89 (q, *J* = 7.0 Hz, 2H, O$\mathbf{CH_2}$CH$_3$), 3.72(s, 3H, OCH$_3$), 2.19 (s, 3H, CH$_3$), 1.11(t, *J* = 7.0 Hz, 3H, OCH$_2$$\mathbf{CH_3}$)

5-Ethoxycarbonyl-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimi-din-2(1H)-one (4d):

Mp 163-165°C[15], IR (KBr) cm^{-1} = 3252and 3108 (N–H str.), 1687 and 1653(C=O str.); 1H NMR: δ=9.46(s, 1H, OH), 9.23 (s, 1H, NH), 7.66 (s, 1H, NH), 7.11-6.62 (m, 4H, C6H4), 5.06(s, 1H, CH), 3.98(q, J = 7.1 Hz, 2H, O$\mathbf{CH_2}$CH3), 2.22(s, 3H, CH3), 1.23(t, J = 7.1 Hz, 3H, OCH$_2$$\mathbf{CH_3}$)

5-Ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimi-din-2(1H)-one (4e):

Mp 231-233°C[14], IR (KBr) cm^{-1} = 3255and 3108 (N–H str.), 1689 and 1650 (C=O str.); ^{1}H NMR: δ=9.40 (s, 1H, OH), 9.14 (s, 1H, NH), 7.58 (s, 1H, NH), 7.01-6.58 (2d, 4H, C$_6$H$_4$), 5.04 (s, 1H, CH), 3.94 (q, *J* = 7.2 Hz, 2H, O$\mathbf{CH_2}$CH$_3$), 2.19 (s, 3H, CH$_3$), 1.12 (t, *J* = 7.2 Hz, 3H, OCH$_2$$\mathbf{CH_3}$)

4-(3-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimi-din-2(1H)-one (4f):

Mp 193-195°C[15]; cm^{-1} = 12 and 3130 (N–H str.), 1697 and 1643 (C=O str.); ^{1}H NMR: δ=9.24(s, 1H, NH), 7.77(s, 1H, NH), 7.36-7.17(m, 4H, C$_6$H$_4$), 5.14(s, 1H, CH), 3.98(q, *J* = 7.0 Hz, 2H, O$\mathbf{CH_2}$CH$_3$), 2.24(s, 3H, CH$_3$), 1.08(t, *J* = 7.0Hz, 3H, OCH$_2$$\mathbf{CH_3}$).

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimi-din-2(1H)-one (4g):

Mp 212-214°C[15], lit.[6] 213-215°C; : IR (KBr) cm^{-}1 = 3245 and 3122 (N–H str.), 1717 and 1652 (C=O str.); ^{1}H NMR: δ=9.19 (s, 1H, NH), 7.81 (s, 1H, NH), 7.36-7.18(2d, 4H, C$_6$H$_4$), 5.02(s, 1H, CH), 3.93(q, *J* = 6.8 Hz, 2H, O$\mathbf{CH_2}$CH$_3$), 2.24(s, 3H, CH$_3$), 1.08(t, *J* = 6.8 Hz, 3H, OCH$_2$$\mathbf{CH_3}$)

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4h):

Mp 208-210°C[15], IR (KBr) cm_1 = 3248 and 3122 (N–H str.), 1711 and 1643 (C=O str.); δ=9.4 (s, 1H, NH), 8.01(s, 1H, NH), 8.25-7.43(2d, 4H, C$_6$H$_4$), 5.30(s, 1H, CH), 3.95 (q, *J* = 7.0 Hz, 2H, O$\mathbf{CH_2}$CH$_3$), 2.19 (s, 3H, CH$_3$), 1.06 (t, *J* = 7.0 Hz, 3H, OCH$_2$$\mathbf{CH_3}$).

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (4i):

Mp 209-211°C[15]; IR (KBr) cm^{-1}, 3249 and 3121 (N–H str.), 1701 (C=O str.) and 1541 (C=S str.); ^{1}H NMR: δ=10.25(s, 1H, NH), 9.55 (s, 1H, NH), 7.37-7.21(m, 5H, C$_6$H$_5$), 5.20 (d, *J* = 3.5 Hz, 1H, CH), 4.02(q, *J* = 7.1 Hz, 2H, O$\mathbf{CH_2}$CH$_3$), 2.16 (s, 3H, CH$_3$), 1.11(t, *J* = 7.1 Hz, 3H, OCH$_2$$\mathbf{CH_3}$)

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimi-din-2(1H)-thione (4j):

Mp 193-195°C[15]; IR (KBr) cm^{-1}, 3257 and 3119 (N–H str.), 1696 (C=O str.) and 1543 (C=S str.); ^{1}H NMR: δ=10.27(s, 1H, NH), 10.01(s, 1H, NH), 7.25-7.01(2d, 4H, C$_6$H$_4$), 5.14 (s, 1H, CH), 4.04 (q, *J* = 7.2 Hz, 2H, O$\mathbf{CH_2}$CH$_3$), 2.27(s, 3H, C$_6$H$_5$-$\mathbf{CH_3}$), 2.25(s, 3H, CH$_3$), 1.06 (t, *J* = 7.2 Hz, 3H, OCH$_2$$\mathbf{CH_3}$).

5-Ethoxycarbonyl -4-(4-methoxylphenyl)- 6-methyl -3,4-dihydropyri-midin-2(1H)-thione (4k):

Mp 149-151°C[15]; IR (KBr) cm^{-}1 = 3251 and 3119 (N–H str.), 1685 (C=O str.) and 1543 (C=S str.); ^{1}H NMR: δ=10.17(s, 1H, NH), 9.55 (s, 1H, NH), 7.16-6.86(2d, 4H, C$_6$H$_4$), 4.98(s, 1H, CH), 4.02 (q, *J* = 6.9 Hz, 2H, O**CH2**CH$_3$), 3.17(s,3H, OCH3), 2.27(s, 3H, CH$_3$), 1.10(t, *J* = 6.9 Hz, 3H, OCH$_2$$\mathbf{CH_3}$).

4-(4-Chlorophenyl)- 5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimi-din-2(1H)-thione (4l):

Mp 193-195°C[15]; IR (KBr) cm^{-}1 = 3254 and 3121 (N–H str.), 1665 (C=O str.) and 1547 (C=S str.); ^{1}H NMR: δ=10.40 (s, 1H, NH), 9.73 (s, 1H, NH), 7.41-7.17 (2d, 4H, C$_6$H$_4$), 5.12 (s, 1H, CH), 4.01(q, *J* = 6.5 Hz, 2H, O$\mathbf{CH_2}$CH$_3$), 2.32 (s, 3H, CH$_3$), 1.12 (t, *J* = 6.5 Hz, 3H, OCH$_2$$\mathbf{CH_3}$).

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl-3,4-dihydropyrimidin-2(1H)-thione (4m):

Mp 109-111°C[15]; IR (KBr) cm^{-}1 = 3247 and 3123 (N–H str.), 1679 (C=O str.) and 1539 (C=S str.); ^{1}H NMR: δ=10.38 (s, 1H, NH), 9.59(s, 1H, NH), 8.23-7.41(2d, 4H, C$_6$H$_4$), 5.32(s, 1H, CH), 4.04(q, *J* = 7.3 Hz, 2H, O$\mathbf{CH_2}$CH$_3$), 2.28(s, 3H, CH$_3$), 1.09 (t, *J* = 7.3 Hz, 3H, OCH$_2$$\mathbf{CH_3}$)

REFERENCES

Al-Zaydi, K.M., R.M. Borik, M.H. Elnagdi, 2009. Studies with arylhydra-zonopyridinones: Synthesis of new arylhydrazono thieno[3,4-c]pyridinones as novel D2T2 dye class; classical verse green methodologies, *Ultrasonics* Sonochemistry, 16(5): 660-668.

Al-Zaydi, K.M., R.M. Borik, R.A. Mekheimer, M.H. Elnagdi, 2010. Green chemistry: A facile synthesis of polyfunctionally substituted thieno[3,4-c]pyridinones and thieno[3,4-d]pyridazinones under neat reaction conditions, *Ultrasonics* Sonochemistry, 17(5): 909-915.

Al-Zaydi, K.M., R.M. Borik, M.H. Elnagdi, 2010. Arylhydrazononitriles as precursors to 2-substituted 1,2,3-triazoles and 4-amino-5-cyano-pyrazole derivatives utilizing microwave and ultrasound irradiation**,** *Green Chemistry Letters and Reviews*, 5(3): 241-250.

Deshmukh, R.R., R. Rajagopal, K.V. Srinivasan, 2001. Chem., Ultrasound promoted C-C bond formation: Heck reaction at ambient conditions in room temperature ionic liquids, Commun., 1544-1545.

Fu, N.Y., Y.F. Yuan, Z. Cao, S.W. Wang, J.T. Wang and C. Peppe, 2002. Indium(III) bromide-catalyzed preparation of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction, Tetrahedron, 58: 4801-4807.

Gaplovsky, A., M. Gaplovsky, S. Toma, J.L. Luche, 2000. Ultrasound Effects on the Photopinacolization of Benzophenone , J. Org. Chem., 65: 8444-8447.

Ghorab, M.M., S.M. Abdel-Gawad, M.S.A. El-Gaby, 2000. Synthesis and evaluation of some new fluorinated hydroquinazoline derivatives as antifungal agents, Farmaco, 55: 249-255.

Holla, B.S., B.S. Rao, B.K. Sarojini and P.M. Akberali, 2004. One pot synthesis of thiazol-odihydropyrimidinones and evaluation of their anticancer activity, Eur. J. Med. Chem., 39: 777-783.

Hu, E.H., D.R. Slider and U.H. Dolling, 1998. Unprecedented Catalytic Three Component One-Pot Condensation Reaction: An Efficient Synthesis of 5-Alkoxy-carbonyl- 4-aryl-3,4-dihydropyrimidin-2(1H)-ones, J. Org. Chem., 63: 3454-3457.

Joshi, R.S., P.G. Mandhane, S.D. Diwakar, C.H. Gill, 2010. Ultrasound assisted green synthesis of bis(indol-3-yl)methanes catalyzed by 1-hexenesulphonic acid sodium salt, Ultrason. Sonochem, 17: 298-300.

Kappe, C.O., 2000. Biologically active dihydropyrimidones of the Biginelli-type - a literature survey, Eur. J. Med. Chem., 35: 1043-1052.

Lenarsic, R., M. Kocevar, S. Polanc, 1999. ZrCl4-Mediated Regioselective Electrophilic Amination of Activated Arenes with New Alkyl Arylamino-carbonyldiazenecarboxylates: Intermolecular and Intramolecular Reactions, J. Org. Chem., 64: 2558.

Mandhane, P.G., R.S. Joshi, D.R. Nagargoje, C.H. Gill, 2010. Ultrasound-promoted greener approach to synthesize α-hydroxy phosphonates catalyzed by potassium dihydrogen phosphate under solvent-free condition, Tetrahedron Lett., 51: 1490-1492.

Rajagopal, R., D.V. Jarikote, K.V. Srinivasan, 2002. Ultrasound promoted Suzuki cross-coupling reactions in ionic liquid at ambient conditions, Chem. Commun., 616-617.

Suslick, K.S., 1988. Ultrasound, its Chemical, Physical and Biological Effects; VCH: Weinheim.